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(54) Title: COMPOUNDS, COMPOSITIONS, AND METHODS

(57) Abstract: Compounds useful for treating cellular proliferative diseases and disorders by modulating the activity of KSP are disclosed.



WO 03/097053 A1

COMPOUNDS, COMPOSITIONS, AND METHODS

FIELD OF THE INVENTION

This invention relates to compounds which are inhibitors of the mitotic kinesin KSP and are useful in the treatment of cellular proliferative diseases, for example
5 cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders, fungal disorders, and inflammation.

BACKGROUND OF THE INVENTION

Among the therapeutic agents used to treat cancer are the taxanes and vinca alkaloids, which act on microtubules. Microtubules are the primary structural element
10 of the mitotic spindle. The mitotic spindle is responsible for distribution of replicate copies of the genome to each of the two daughter cells that result from cell division. It is presumed that disruption of the mitotic spindle by these drugs results in inhibition of cancer cell division, and induction of cancer cell death. However, microtubules form other types of cellular structures, including tracks for intracellular transport in
15 nerve processes. Because these agents do not specifically target mitotic spindles, they have side effects that limit their usefulness.

Improvements in the specificity of agents used to treat cancer is of considerable interest because of the therapeutic benefits which would be realized if the side effects associated with the administration of these agents could be reduced.
20 Traditionally, dramatic improvements in the treatment of cancer are associated with identification of therapeutic agents acting through novel mechanisms. Examples of this include not only the taxanes, but also the camptothecin class of topoisomerase I inhibitors. From both of these perspectives, mitotic kinesins are attractive targets for new anti-cancer agents.

25 Mitotic kinesins are enzymes essential for assembly and function of the mitotic spindle, but are not generally part of other microtubule structures, such as in nerve processes. Mitotic kinesins play essential roles during all phases of mitosis. These enzymes are "molecular motors" that transform energy released by hydrolysis of ATP into mechanical force which drives the directional movement of cellular cargoes along
30 microtubules. The catalytic domain sufficient for this task is a compact structure of approximately 340 amino acids. During mitosis, kinesins organize microtubules into the bipolar structure that is the mitotic spindle. Kinesins mediate movement of chromosomes along spindle microtubules, as well as structural changes in the mitotic

spindle associated with specific phases of mitosis. Experimental perturbation of mitotic kinesin function causes malformation or dysfunction of the mitotic spindle, frequently resulting in cell cycle arrest and cell death.

Among the mitotic kinesins which have been identified is KSP. KSP belongs
5 to an evolutionarily conserved kinesin subfamily of plus end-directed microtubule motors that assemble into bipolar homotetramers consisting of antiparallel homodimers. During mitosis KSP associates with microtubules of the mitotic spindle. Microinjection of antibodies directed against KSP into human cells prevents spindle pole separation during prometaphase, giving rise to monopolar spindles and causing
10 mitotic arrest and induction of programmed cell death. KSP and related kinesins in other, non-human, organisms, bundle antiparallel microtubules and slide them relative to one another, thus forcing the two spindle poles apart. KSP may also mediate in anaphase B spindle elongation and focussing of microtubules at the spindle pole.

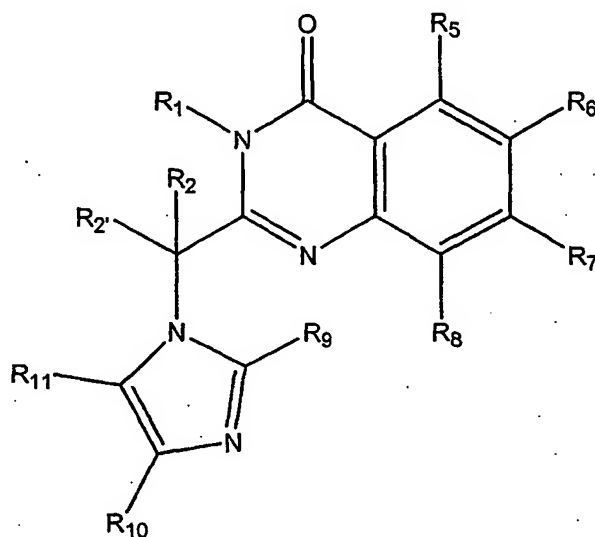
Human KSP (also termed HsEg5) has been described (Blangy, et al., Cell,
15 83:1159-69 (1995); Whitehead, et al., Arthritis Rheum., 39:1635-42 (1996); Galgio et al., J. Cell Biol., 135:339-414 (1996); Blangy, et al., J Biol. Chem., 272:19418-24 (1997); Blangy, et al., Cell Motil Cytoskeleton, 40:174-82 (1998); Whitehead and Rattner, J. Cell Sci., 111:2551-61 (1998); Kaiser, et al., JBC 274:18925-31 (1999); GenBank accession numbers: X85137, NM004523 and U37426), and a fragment of
20 the KSP gene (TRIP5) has been described (Lee, et al., Mol Endocrinol., 9:243-54 (1995); GenBank accession number L40372). Xenopus KSP homologs (Eg5), as well as Drosophila KLP61 F/KRP1 30 have been reported.

Mitotic kinesins, including KSP, are attractive targets for the discovery and development of novel antimitotic chemotherapeutics. Accordingly, it is an object of
25 the present invention to provide compounds, compositions and methods useful in the inhibition of KSP.

SUMMARY OF THE INVENTION

In accordance with the objects outlined above, the present invention provides compounds that can be used to treat cellular proliferative diseases. The compounds
30 are KSP inhibitors, particularly human KSP inhibitors. The present invention also provides compositions comprising such compounds, and methods utilizing such compounds or compositions, which can be used to treat cellular proliferative diseases. In one aspect, the invention relates to methods for treating cellular proliferative

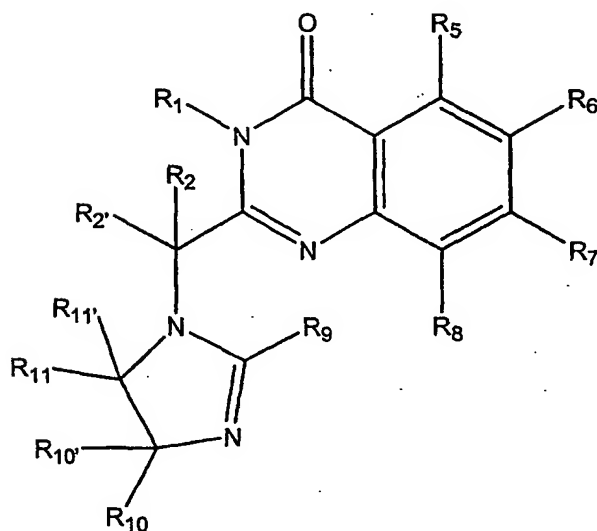
diseases, and for treating disorders by inhibiting the activity of KSP. The methods employ compounds represented by Formula Ia or Ib:



Formula Ia

5

or



Formula Ib

10 wherein:

R_1 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aryl- C_1 - C_4 -alkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaryl- C_1 - C_4 -alkyl-;
 R_2 and R_2' are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aryl- C_1 - C_4 -alkyl-,

15

optionally substituted heteroaryl-, and optionally substituted heteroaryl-C₁-C₄-alkyl-; or R₂ and R₂' taken together form an optionally substituted 3- to 7-membered ring;

5 R₅, R₆, R₇ and R₈ are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted alkoxy, halogen, hydroxyl-, nitro, cyano, dialkylamino, alkylsulfonyl-, alkylsulfonamido, alkylthio, carboxyalkyl-, carboxamido, aminocarbonyl-, optionally substituted aryl-, optionally substituted aryloxy, optionally substituted heteroaryl-, and optionally substituted heteroaryloxy;

10 R₉ is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, and optionally substituted heteroaryl-; and

R₁₀, R₁₀', R₁₁, and R₁₁' are independently hydrogen, optionally substituted alkyl-, optionally substituted aryl-, or optionally substituted aralkyl-,

15 (Formula Ia or Ib including single stereoisomers and mixtures of stereoisomers);

pharmaceutically acceptable salts of a compound of Formula Ia or Ib;

pharmaceutically acceptable solvates of a compound of Formula Ia or Ib; and

20 pharmaceutically acceptable solvates of a pharmaceutically acceptable salt of a compound of Formula Ia or Ib.

In one aspect, the invention relates to methods for treating cellular proliferative diseases and other disorders that can be treated by inhibiting KSP by the administration of a therapeutically effective amount of a compound of Formula Ia or Ib; a pharmaceutically acceptable salt of a compound of Formula Ia or Ib;

25 pharmaceutically acceptable solvate of a compound of Formula Ia or Ib; or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of a compound of Formula Ia or Ib. Such diseases and disorders include cancer, hyperplasia, restenosis, cardiac hypertrophy, immune disorders, fungal disorders and inflammation.

30 In another aspect, the invention relates to compounds useful in inhibiting KSP kinesin. The compounds have the structures shown above in Formula Ia or Ib; a pharmaceutically acceptable salt of a compound of Formula Ia or Ib; a pharmaceutically acceptable solvate of a compound of Formula Ia or Ib; or a

pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of a compound of Formula Ia or Ib. The invention also relates to pharmaceutical compositions comprising: a therapeutically effective amount of a compound of Formula Ia or Ib; a pharmaceutically acceptable salt of a compound of Formula Ia or Ib; a pharmaceutically acceptable solvate of a compound of Formula Ia or Ib; or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of a compound of Formula Ia or Ib; and one or more pharmaceutical excipients. In another aspect, the composition further comprises a chemotherapeutic agent other than a compound of the present invention.

10 In an additional aspect, the present invention provides methods of screening for compounds that will bind to a KSP kinesin, for example compounds that will displace or compete with the binding of a compound of the invention. The methods comprise combining a labeled compound of the invention, a KSP kinesin, and at least one candidate agent and determining the binding of the candidate agent to the KSP
15 kinesin.

In a further aspect, the invention provides methods of screening for modulators of KSP kinesin activity. The methods comprise combining a compound of the invention, a KSP kinesin, and at least one candidate agent and determining the effect of the candidate agent on the KSP kinesin activity.

20 DETAILED DESCRIPTION OF THE INVENTION

Definitions

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise. The following abbreviations
25 and terms have the indicated meanings throughout:

Ac.	=	acetyl
Boc	=	t-butyloxy carbonyl
Bu	=	butyl
c-	=	cyclo
30 CBZ	=	carbobenzoxo = benzyloxycarbonyl
DCM	=	dichloromethane = methylene chloride = CH ₂ Cl ₂
DIEA	=	N,N-diisopropylethylamine
DMF	=	N,N-dimethylformamide

- DMSO = dimethyl sulfoxide
 Et = ethyl
 Fmoc = 9-fluorenylmethoxycarbonyl
 GC = gas chromatography
 5 HOAc = acetic acid
 Me = methyl
 mesyl = methanesulfonyl
 PEG = polyethylene glycol
 Ph = phenyl
 10 PhOH = phenol
 Pht = phthalyl
 Py = pyridine
 rt or RT = room temperature
 sat'd = saturated
 15 s- = secondary
 t- = tertiary
 TFA = trifluoroacetic acid
 THF = tetrahydrofuran
 tosyl = p-toluenesulfonyl
 20 **Alkyl** is intended to include linear, branched, or cyclic aliphatic hydrocarbon structures and combinations thereof, which structures may be saturated or unsaturated. **Lower-alkyl** refers to alkyl groups of from 1 to 5 carbon atoms, preferably from 1 to 4 carbon atoms. Examples of lower-alkyl groups include methyl-, ethyl-, propyl-, isopropyl-, butyl-, s-and t-butyl- and the like. Preferred alkyl groups are those of C₂₀ or below. More preferred alkyl groups are those of C₁₃ or below. **Cycloalkyl** is a subset of alkyl and includes cyclic aliphatic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkyl groups include c- propyl-, c-butyl-, c-pentyl-, norbornyl-, adamantyl- and the like. **Cycloalkyl-alkyl-** is another subset of alkyl and refers to cycloalkyl attached to the parent structure through a non-cyclic alkyl-.
 25 Examples of cycloalkyl-alkyl- include cyclohexylmethyl-, cyclopropylmethyl-, cyclohexylpropyl-, and the like. In this application, alkyl includes alkanyl-, alkenyl- and alkynyl- residues; it is intended to include vinyl-, allyl-, isoprenyl- and the like. When an alkyl residue having a specific number of carbons is named, all geometric

isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl-, sec-butyl-, isobutyl- and t-butyl-; "propyl" includes n-propyl-, isopropyl-, and c-propyl-.

Alkylene-, alkenylene-, and alkynylene- are other subsets of alkyl-, including
5 the same residues as alkyl-, but having two points of attachment within a chemical structure. Examples of alkylene include ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), dimethylpropylene ($-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$) and cyclohexylpropylene ($-\text{CH}_2\text{CH}_2\text{CH}(\text{C}_6\text{H}_{13})-$). Likewise, examples of alkenylene include ethenylene ($-\text{CH}=\text{CH}-$), propenylene ($-\text{CH}=\text{CH}-\text{CH}_2-$), and cyclohexylpropenylene ($-\text{CH}=\text{CHCH}(\text{C}_6\text{H}_{13})-$). Examples of alkynylene include ethynylene ($-\text{C}\equiv\text{C}-$) and
10 propynylene ($-\text{CH}\equiv\text{CH}-\text{CH}_2-$).

Cycloalkenyl is a subset of alkyl and includes unsaturated cyclic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkenyl groups include c-hexenyl-, c-pentenyl- and the like.

15 Alkoxy or alkoxyl refers to an alkyl group, preferably including from 1 to 8 carbon atoms, of a straight, branched, or cyclic configuration, or a combination thereof, attached to the parent structure through an oxygen (i.e., the group alkyl-O-). Examples include methoxy-, ethoxy-, propoxy-, isopropoxy-, cyclopropyloxy-, cyclohexyloxy- and the like. Lower-alkoxy refers to alkoxy groups containing one to
20 four carbons.

Acyl refers to groups of from 1 to 8 carbon atoms of a straight, branched, or cyclic configuration or a combination thereof, attached to the parent structure through a carbonyl functionality. Such groups may be saturated or unsaturated, and aliphatic or aromatic. One or more carbons in the acyl residue may be replaced by oxygen,
25 nitrogen (e.g., carboxamido), or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl-, benzoyl-, propionyl-, isobutyryl-, oxalyl-, t-butoxycarbonyl-, benzyloxycarbonyl-, morpholinylcarbonyl-, and the like. Lower-acyl refers to acyl groups containing one to four carbons.

Amino refers to the group $-\text{NH}_2$. The term "substituted amino" refers to the
30 group $-\text{NHR}$ or $-\text{NRR}$ where each R is independently selected from the group: optionally substituted alkyl-, optionally substituted alkoxy, optionally substituted aminocarbonyl-, optionally substituted aryl-, optionally substituted heteroaryl-, optionally substituted heterocyclyl-, acyl-, alkoxycarbonyl-, sulfanyl-, sulfinyl- and

sulfonyl-, e.g., diethylamino, methylsulfonylamino, furanyl-oxy-sulfonamino.

Aminocarbonyl- refers to the group $-NR^cCOR^b$, $-NR^cCO_2R^a$, or $-NR^cCONR^bR^c$, where

R^a is optionally substituted C_1 - C_6 alkyl-, aryl-, heteroaryl-, aryl- C_1 - C_4 alkyl-, or heteroaryl- C_1 - C_4 alkyl- group;

R^b is H or optionally substituted C_1 - C_6 alkyl-, aryl-, heteroaryl-, aryl- C_1 - C_4 alkyl-, or heteroaryl- C_1 - C_4 alkyl- group; and

R^c is hydrogen or C_1 - C_4 alkyl-; and

where each optionally substituted R^b group is independently unsubstituted or

substituted with one or more substituents independently selected from C_1 - C_4 alkyl-, aryl-, heteroaryl-, aryl- C_1 - C_4 alkyl-, heteroaryl- C_1 - C_4 alkyl-, C_1 - C_4 haloalkyl-, $-OC_1$ - C_4 alkyl-, $-OC_1$ - C_4 alkylphenyl-, $-C_1$ - C_4 alkyl-OH, $-OC_1$ - C_4 haloalkyl-, halogen, -OH, $-NH_2$, $-C_1$ - C_4 alkyl- NH_2 , $-N(C_1$ - C_4 alkyl)(C_1 - C_4 alkyl), $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl)(C_1 - C_4 alkylphenyl), $-NH(C_1$ - C_4 alkylphenyl), cyano, nitro, oxo (as a substituent for heteroaryl), $-CO_2H$, $-C(O)OC_1$ - C_4 alkyl-, $-CON(C_1$ - C_4 alkyl)(C_1 - C_4 alkyl), $-CONH(C_1$ - C_4 alkyl), $-CONH_2$, $-NHC(O)(C_1$ - C_4 alkyl), $-NHC(O)(phenyl)$, $-N(C_1$ - C_4 alkyl) $C(O)(C_1$ - C_4 alkyl), $-N(C_1$ - C_4 alkyl) $C(O)(phenyl)$, $-C(O)C_1$ - C_4 alkyl-, $-C(O)C_1$ - C_4 phenyl-, $-C(O)C_1$ - C_4 haloalkyl-, $-OC(O)C_1$ - C_4 alkyl-, $-SO_2(C_1$ - C_4 alkyl), $-SO_2(phenyl)$, $-SO_2(C_1$ - C_4 haloalkyl), $-SO_2NH_2$, $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2NH(phenyl)$, $-NHSO_2(C_1$ - C_4 alkyl), $-NHSO_2(phenyl)$, and $-NHSO_2(C_1$ - C_4 haloalkyl).

Antimitotic refers to a drug for inhibiting or preventing mitosis, for example, by causing metaphase arrest. Some antitumour drugs block proliferation and are considered antimitotics.

Aryl and **heteroaryl** mean a 5- or 6-membered aromatic or heteroaromatic ring containing 0 or 1-4 heteroatoms, respectively, selected from O, N, or S; a bicyclic 9- or 10-membered aromatic or heteroaromatic ring system containing 0 or 1-4 (or more) heteroatoms, respectively, selected from O, N, or S; or a tricyclic 12- to 14-membered aromatic or heteroaromatic ring system containing 0 or 1-4 (or more) heteroatoms, respectively, selected from O, N, or S. The aromatic 6- to 14-membered carbocyclic rings include, e.g., phenyl-, naphthyl-, indanyl-, tetralinyl-, and fluorenyl- and the 5- to 10-membered aromatic heterocyclic rings include, e.g., imidazolyl-, pyridinyl-, indolyl-, thienyl-, benzopyranonyl-, thiazolyl-, furanyl-, benzimidazolyl-,

quinoliny-, isoquinoliny-, quinoxaliny-, pyrimidiny-, pyraziny-, tetrazoly- and pyrazoly-.

Aralkyl- refers to a residue in which an aryl moiety is attached to the parent structure via an alkyl residue. Examples include benzyl-, phenethyl-, phenylvinyl-, phenylallyl- and the like. **Heteroaralkyl-** refers to a residue in which a heteroaryl moiety is attached to the parent structure via an alkyl residue. Examples include furanylmethyl-, pyridinylmethyl-, pyrimidinylethyl- and the like.

Aralkoxy- refers to the group -O-aralkyl. Similarly, **heteroaralkoxy-** refers to the group -O-heteroaralkyl-; **aryloxy-** refers to the group -O-aryl-; **acyloxy-** refers to the group -O-acyl-; **heteroaryloxy-** refers to the group -O-heteroaryl-; and **heterocyclyloxy-** refers to the group -O-heterocyclyl (i.e., aralkyl-, heteroaralkyl-, aryl-, acyl-, heterocyclyl-, or heteroaryl is attached to the parent structure through an oxygen).

Carboxyalkyl- refers to the group -alkyl-COOH.

Carboxamido refers to the group -CONR^bR^c, where

R^b is H or optionally substituted C₁-C₆ alkyl-, aryl-, heteroaryl-, aryl-C₁-C₄ alkyl-, or heteroaryl-C₁-C₄ alkyl- group; and

R^c is hydrogen or C₁-C₄ alkyl-; and

where each optionally substituted R^b group is independently unsubstituted or substituted with one or more substituents independently selected from C₁-C₄ alkyl-, aryl-, heteroaryl-, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl-, -OC₁-C₄ alkylphenyl-, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl-, halogen, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl-, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl-, -C(O)C₁-C₄ phenyl-, -C(O)C₁-C₄ haloalkyl-, -OC(O)C₁-C₄ alkyl-, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl). Carboxamido is meant to include carbamoyl-; lower-alkyl carbamoyl-;

benzylcarbamoyl-; phenylcarbamoyl-; methoxymethyl-carbamoyl-; and the like.

Halogen or **halo** refers to fluorine, chlorine, bromine or iodine. Fluorine, chlorine and bromine are preferred. Dihaloaryl-, dihaloalkyl-, trihaloaryl- etc. refer to
5 aryl and alkyl substituted with the designated plurality of halogens (here, 2, 2 and 3, respectively), but not necessarily a plurality of the same halogen; thus 4-chloro-3-fluorophenyl- is within the scope of dihaloaryl-.

Heterocyclyl means a cycloalkyl or aryl residue in which one to four of the carbons is replaced by a heteroatom such as oxygen, nitrogen or sulfur. Examples of
10 heterocycles that fall within the scope of the invention include azetidiny-, imidazolinyl-, pyrrolidinyl-, pyrazolyl-, pyrrolyl-, indolyl-, quinolinyl-, isoquinolinyl-, tetrahydroisoquinolinyl-, benzofuranyl-, benzodioxanyl-, benzodioxyl- (commonly referred to as methylenedioxyphenyl-, when occurring as a substituent), tetrazolyl-, morpholinyl-, thiazolyl-, pyridinyl-, pyridazinyl-, piperidinyl-, pyrimidinyl-, thienyl-,
15 furanyl-, oxazolyl-, oxazolinyl-, isoxazolyl-, dioxanyl-, tetrahydrofuranyl- and the like. "N-heterocyclyl" refers to a nitrogen-containing heterocycle. The term heterocyclyl encompasses heteroaryl-, which is a subset of heterocyclyl-. Examples of N-heterocyclyl residues include azetidiny-, 4-morpholinyl-, 4-thiomorpholinyl-, 1-piperidinyl-, 1-pyrrolidinyl-, 3-thiazolidinyl-, piperazinyl- and
20 4-(3,4-dihydrobenzoxazinyl). Examples of substituted heterocyclyl include 4-methyl-1-piperazinyl- and 4-benzyl-1-piperidinyl-.

A **leaving group** or **atom** is any group or atom that will, under the reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Suitable examples of such groups unless otherwise specified are halogen atoms,
25 mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

Optional or **optionally** means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where said event or circumstances occurs and instances in which it does not. For example, "optionally substituted alkyl" includes "alkyl" and "substituted alkyl" as defined
30 herein. It will be understood by those skilled in the art with respect to any group containing one or more substituents that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical and/or synthetically non-feasible and/or inherently unstable.

Substituted alkoxy refers to alkoxy wherein the alkyl constituent is substituted (i.e., -O-(substituted alkyl)). One suitable substituted alkoxy group is "polyalkoxy" or -O-(optionally substituted alkylene)-(optionally substituted alkoxy), and includes groups such as -OCH₂CH₂OCH₃, and residues of glycol ethers such as polyethyleneglycol, and -O(CH₂CH₂O)_xCH₃, where x is an integer of about 2-20, preferably about 2-10, and more preferably about 2-5. Another suitable substituted alkoxy group is hydroxyalkoxy or -OCH₂(CH₂)_yOH, where y is an integer of about 1-10, preferably about 1-4.

Substituted- alkyl-, aryl-, and heteroaryl- refer respectively to alkyl-, aryl-, and heteroaryl wherein one or more (up to about 5, preferably up to about 3) hydrogen atoms are replaced by a substituent independently selected from the group: -R^a, -OR^b, -O(C₁-C₂ alkyl)O- (as an aryl substituent), -SR^b, -NR^bR^c, halogen, cyano, nitro, -COR^b, -CO₂R^b, -CONR^bR^c, -OCOR^b, -OCO₂R^a, -OCONR^bR^c, -NR^cCOR^b, -NR^cCO₂R^a, -NR^cCONR^bR^c, -CO₂R^b, -CONR^bR^c, -NR^cCOR^b, -SOR^a, -SO₂R^a, -SO₂NR^bR^c, and -NR^cSO₂R^a.

where R^a is an optionally substituted C₁-C₆ alkyl-, aryl-, heteroaryl-, aryl-C₁-C₄ alkyl-, or heteroaryl-C₁-C₄ alkyl- group,

R^b is H or optionally substituted C₁-C₆ alkyl-, aryl-, heteroaryl-, aryl-C₁-C₄ alkyl-, or heteroaryl-C₁-C₄ alkyl- group;

R^c is hydrogen or C₁-C₄ alkyl-;

where each optionally substituted R^a group and R^b group is independently unsubstituted or substituted with one or more substituents independently selected from C₁-C₄ alkyl-, aryl-, heteroaryl-, aryl-C₁-C₄ alkyl-, heteroaryl-C₁-C₄ alkyl-, C₁-C₄ haloalkyl-, -OC₁-C₄ alkyl-, -OC₁-C₄ alkylphenyl-, -C₁-C₄ alkyl-OH, -OC₁-C₄ haloalkyl-, halogen, -OH, -NH₂, -C₁-C₄ alkyl-NH₂, -N(C₁-C₄ alkyl)(C₁-C₄ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)(C₁-C₄ alkylphenyl), -NH(C₁-C₄ alkylphenyl), cyano, nitro, oxo (as a substituent for heteroaryl), -CO₂H, -C(O)OC₁-C₄ alkyl-, -CON(C₁-C₄ alkyl)(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CONH₂, -NHC(O)(C₁-C₄ alkyl), -NHC(O)(phenyl), -N(C₁-C₄ alkyl)C(O)(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)C(O)(phenyl), -C(O)C₁-C₄ alkyl, -C(O)C₁-C₄ phenyl-, -C(O)C₁-C₄ haloalkyl-, -OC(O)C₁-C₄ alkyl-, -SO₂(C₁-C₄ alkyl), -SO₂(phenyl), -SO₂(C₁-C₄ haloalkyl), -SO₂NH₂, -SO₂NH(C₁-C₄ alkyl), -SO₂NH(phenyl), -

NHSO₂(C₁-C₄ alkyl), -NHSO₂(phenyl), and -NHSO₂(C₁-C₄ haloalkyl).

Sulfanyl refers to the groups: -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl), and -S-(optionally substituted heterocyclyl).

- 5 **Sulfinyl** refers to the groups: -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl), -S(O)-(optionally substituted heterocyclyl); and -S(O)-(optionally substituted amino).

- Sulfonyl** refers to the groups: -S(O₂)-H, -S(O₂)-(optionally substituted alkyl), -S(O₂)-(optionally substituted aryl), -S(O₂)-(optionally substituted heteroaryl),
 10 -S(O₂)-(optionally substituted heterocyclyl), -S(O₂)-(optionally substituted alkoxy), -S(O₂)-(optionally substituted aryloxy), -S(O₂)-(optionally substituted heteroaryloxy), -S(O₂)-(optionally substituted heterocycloxy); and -S(O₂)-(optionally substituted amino).

- Pharmaceutically acceptable salts** refers to those salts that retain the
 15 biological effectiveness of the free compound and that are not biologically undesirable or unsuitable for pharmaceutical use, formed with a suitable acid or base, and includes pharmaceutically acceptable acid addition salts and base addition salts.

- Pharmaceutically acceptable acid addition salts** include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid,
 20 phosphoric acid and the like, and those derived from organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

- Pharmaceutically acceptable base addition salts** include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particular embodiments are the ammonium, potassium, sodium, calcium, and magnesium salts. Base addition salts also include those derived from pharmaceutically acceptable organic non-toxic
 25 bases, including salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine.

Protecting group has the meaning conventionally associated with it in organic synthesis, i.e. a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999), which is incorporated herein by reference in its entirety. For example, a hydroxy protected form is where at least one of the hydroxyl groups present in a compound is protected with a hydroxy protecting group. Likewise, amines and other reactive groups may similarly be protected.

Solvate refers to the compound formed by the interaction of a solvent and a compound of Formula Ia or Ib or salt thereof. Suitable solvates of the compounds of the Formula Ia or Ib or a salt thereof are pharmaceutically acceptable solvates including hydrates.

Many of the compounds described herein contain one or more asymmetric centers (e.g. the carbon to which R_2 and R_2' are attached where R_2 differs from R_2') and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms and rotational isomers are also intended to be included.

When desired, the R- and S-isomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallization; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid

chromatography in a chiral environment, for example on a chiral support, such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step may be required to liberate the desired enantiomeric form. Alternatively, specific enantiomer may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

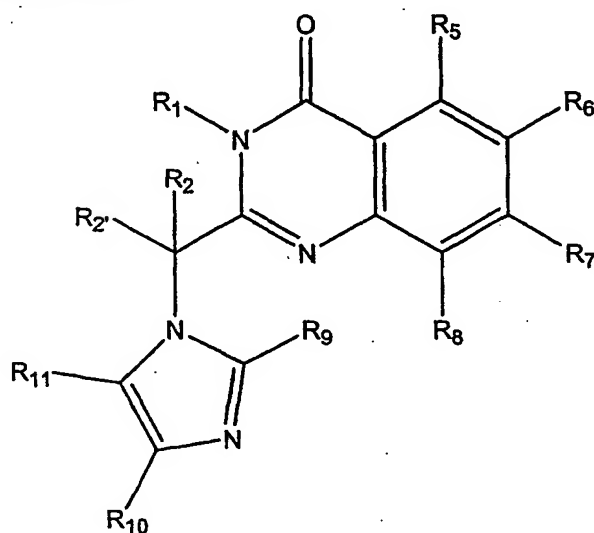
Compounds of the Present Invention

The present invention is directed to a class of novel compounds, that can be described as quinazolinone derivatives, that are inhibitors of one or more mitotic kinesins. By inhibiting mitotic kinesins, but not other kinesins (e.g., transport kinesins), specific inhibition of cellular proliferation is accomplished. While not intending to be bound by any theory, the present invention capitalizes on the finding that perturbation of mitotic kinesin function causes malformation or dysfunction of mitotic spindles, frequently resulting in cell cycle arrest and cell death. According to one embodiment of the invention, the compounds described herein inhibit the mitotic kinesin, KSP, particularly human KSP. In another embodiment, the compounds inhibit the mitotic kinesin, KSP, as well as modulating one or more of the human mitotic kinesins selected from the group consisting of HSET (see, U.S. Patent No. 6,361,993, which is incorporated herein by reference); MCAK (see, U.S. Patent No. 6,331,424, which is incorporated herein by reference); CENP-E (see, PCT Publication No. WO 99/13061, which is incorporated herein by reference); Kif4 (see, U.S. Patent No. 6,440,684, which is incorporated herein by reference); MKLP1 (see, U.S. Patent No. 6,448,025, which is incorporated herein by reference); Kif15 (see, U.S. Patent No. 6,355,466, which is incorporated herein by reference); Kid (see, U.S. Patent No. 6,387,644, which is incorporated herein by reference); Mpp1, CMKrp, KinI-3 (see, U.S. Patent No. 6,461,855, which is incorporated herein by reference); Kip3a (see, PCT Publication No. WO 01/96593, which is incorporated herein by reference); Kip3d (see, U.S. Patent No. 6,492,151, which is incorporated herein by reference); and RabK6.

The methods of inhibiting a mitotic kinesin comprise contacting an inhibitor of the invention with a kinesin, particularly a human kinesin, more particularly, human

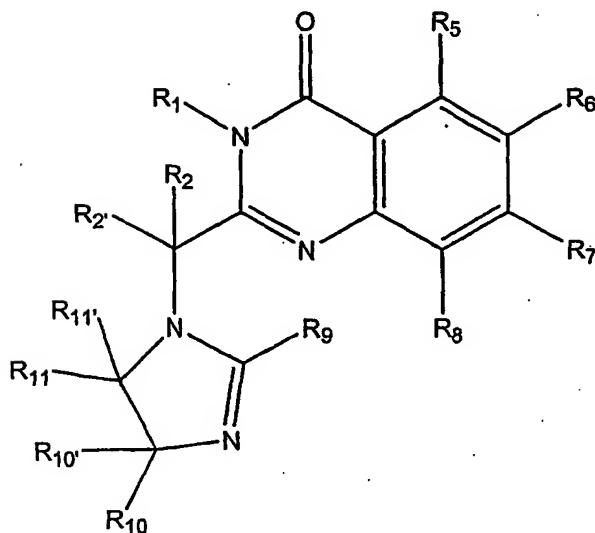
KSP or fragments and variants thereof. The inhibition can be of the ATP hydrolysis activity of the KSP kinesin and/or the mitotic spindle formation activity, such that the mitotic spindles are disrupted. Meiotic spindles may also be disrupted.

- The present invention provides inhibitors of mitotic kinesins, in particular KSP and especially human KSP, for the treatment of disorders associated with cell proliferation. The compounds, compositions and methods are used to treat diseases of cellular proliferation, including, but not limited to cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders, fungal disorders and inflammation. Accordingly, the present invention relates to methods employing compounds represented by Formula Ia or Ib:



Formula Ia

or



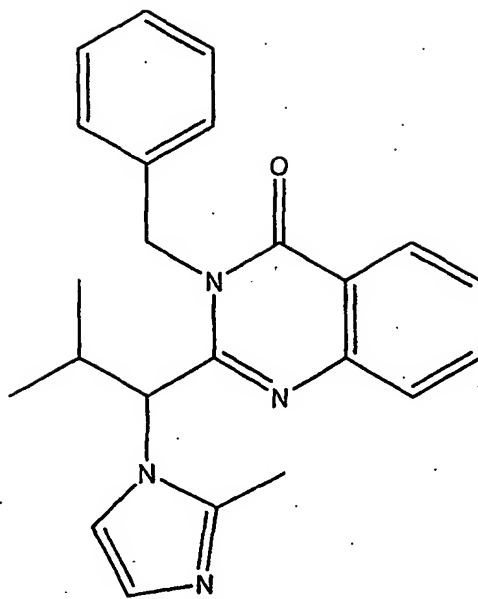
Formula Ib

wherein

- 5 R_1 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaralkyl-;
- R_2 and $R_{2'}$ are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaralkyl-; or R_2 and $R_{2'}$ taken together form an optionally substituted 3- to 7-membered ring;
- 10 R_5 , R_6 , R_7 and R_8 are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted alkoxy, halogen, hydroxyl-, nitro, cyano, dialkylamino, alkylsulfonyl-, alkylsulfonamido, alkylthio, carboxyalkyl-, carboxamido, aminocarbonyl-, optionally substituted aryl-, optionally substituted aryloxy, optionally substituted heteroaryl-, and
- 15 optionally substituted heteroaryloxy;
- R_9 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, and optionally substituted heteroaryl-; and
- R_{10} , $R_{10'}$, R_{11} , and $R_{11'}$ are independently hydrogen, optionally substituted
- 20 alkyl-, optionally substituted aryl-, or optionally substituted aralkyl-, including single stereoisomers and mixtures of stereoisomers;
- pharmaceutically acceptable salts of a compound of Formula Ia or Ib;
- pharmaceutically acceptable solvates of a compound of Formula Ia or Ib; and
- pharmaceutically acceptable solvates of a pharmaceutically acceptable salt of a
- 25 compound of Formula Ia or Ib. In a particular embodiment, the stereogenic center to which R_2 and $R_{2'}$ are attached is of the R configuration.

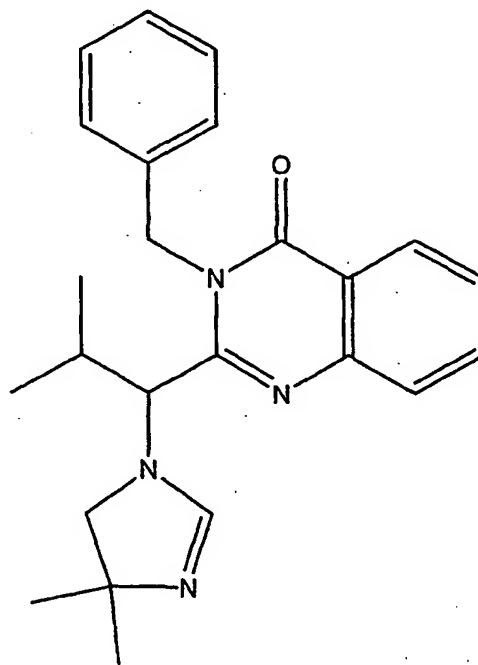
Nomenclature

- The compounds of Formula Ia or Ib can be named and numbered in the manner (e.g., using AutoNom version 2.1 in ChemDraw or ISIS-DRAW) described
- 30 below. For example, the compound:



i.e., the compound according to Formula Ia where R_1 is benzyl-, R_2 is propyl- (or i -
 propyl-), $R_{2'}$ is hydrogen; R_5 , R_6 , R_7 , R_8 , R_{10} , and R_{11} are hydrogen; and R_9 is methyl-
 5 can be named 3-benzyl-2-[2-methyl-1-(2-methyl-imidazol-1-yl)-propyl]-3*H*-
 quinazolin-4-one.

The compound having the structure



10

i.e., the compound according to Formula Ib where R_1 is benzyl-, R_2 is propyl- (or i-

propyl-), R₂' is hydrogen; R₅, R₆, R₇, R₈, R₉, R₁₁, and R₁₁' are hydrogen; and R₁₀ and R₁₀' are methyl- can be named 3-benzyl-2-[1-(4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one.

Synthetic Reaction Parameters

- 5 The compounds of Formula Ia or Ib can be prepared by following the procedures described with reference to the Reaction Schemes below.

Unless specified otherwise, the terms "solvent", "inert organic solvent" or "inert solvent" mean a solvent inert under the conditions of the reaction being described in conjunction therewith [including, for example, benzene, toluene, 10 acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like]. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert organic solvents.

- The term "q.s." means adding a quantity sufficient to achieve a stated function, 15 e.g., to bring a solution to the desired volume (i.e., 100%).

In general, esters of carboxylic acids may be prepared by conventional esterification procedures, for example alkyl esters may be prepared by treating the required carboxylic acid with the appropriate alkanol, generally under acidic conditions. Likewise, amides may be prepared using conventional amidation 20 procedures, for example amides may be prepared by treating an activated carboxylic acid with the appropriate amine. Alternatively, a lower-alkyl ester such as a methyl ester of the acid may be treated with an amine to provide the required amide, optionally in presence of trimethylaluminum following the procedure described in Tetrahedron Lett. 48, 4171-4173, (1977). Carboxyl groups may be protected as alkyl 25 esters, for example methyl esters, which esters may be prepared and removed using conventional procedures, one convenient method for converting carbomethoxy to carboxyl is to use aqueous lithium hydroxide.

The salts and solvates of the compounds mentioned herein may as required be produced by methods conventional in the art. For example, if an inventive compound 30 is an acid, a desired base addition salt can be prepared by treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary, or tertiary); an alkali metal or alkaline earth metal hydroxide; or the like. Illustrative examples of suitable salts include organic salts derived from amino acids such as glycine and

arginine; ammonia; primary, secondary, and tertiary amines; such as ethylenediamine, and cyclic amines, such as cyclohexylamine, piperidine, morpholine, and piperazine; as well as inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

- 5 If a compound is a base, a desired acid addition salt may be prepared by any suitable method known in the art, including treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, pyranosidyl acid, such as glucuronic acid or galacturonic acid, alpha-hydroxy acid, such as citric acid or tartaric acid, amino acid, such as aspartic acid or glutamic acid, aromatic acid, such as benzoic acid or cinnamic acid, sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, or the like.
- 10
- 15 Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples hereinbelow. However, other equivalent separation or isolation procedures can, of course, also be used.
- 20

Synthesis of the Compounds of Formula Ia and Ib

- The compounds of Formula Ia and Ib can be prepared by following the procedures described in PCT Patent Application Serial No. US03/04713; PCT Publication Nos. WO 01/98278 and WO 01/30768, each of which is incorporated herein by reference for all purposes and with reference to the Reaction Schemes below.
- 25

Brief Description Of Reaction Schemes

- Reaction Scheme 1 illustrates synthesis of compounds of Formula 107 which are useful as intermediates in the synthesis of compounds of Formula Ia and Ib.
- 30

Reaction Schemes 2 and 3 illustrate the synthesis of compounds of Formula Ia from compounds of Formula 107.

Reaction Schemes 4 and 5 illustrate the synthesis of compounds of Formula Ib

from compounds of Formula 107.

Reaction Scheme 6 illustrates the synthesis of compounds of Formula 603.

Reaction Scheme 7 illustrates the synthesis of compounds of Formula Ib from compounds of Formula 107.

5 Reaction Scheme 8 illustrates the synthesis of compounds of Formula 107 which are useful as intermediates in the synthesis of compounds of Formula Ia and Ib.

Reaction Scheme 9 illustrates the synthesis of compounds of Formula 809 which are useful as intermediates in the synthesis of compounds of Formula Ia and Ib.

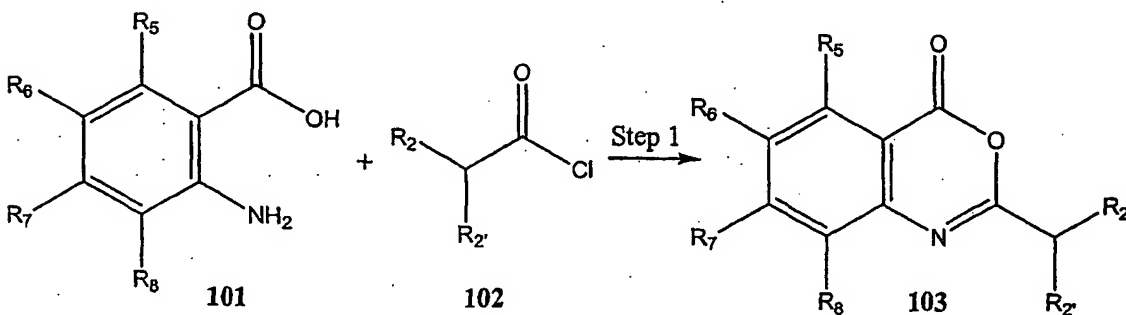
10 Reaction Scheme 10 illustrates the synthesis of compounds of Formula 107 which are useful as intermediates in the synthesis of compounds of Formula Ia and Ib.

Starting Materials

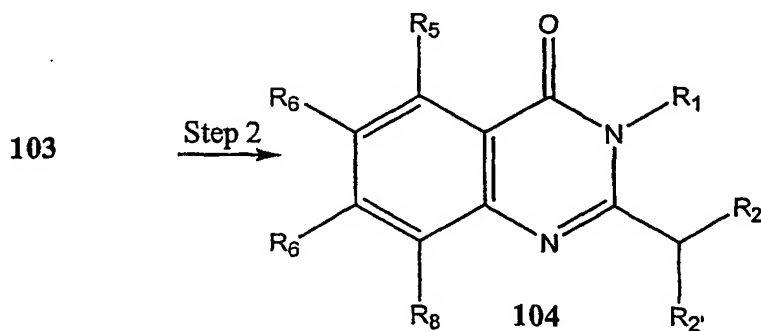
The optionally substituted benzoic acids of Formula 101 and the other reagents are commercially available, e.g., from Aldrich Chemical Company, Milwaukee, WI or may be readily prepared by those skilled in the art using commonly employed

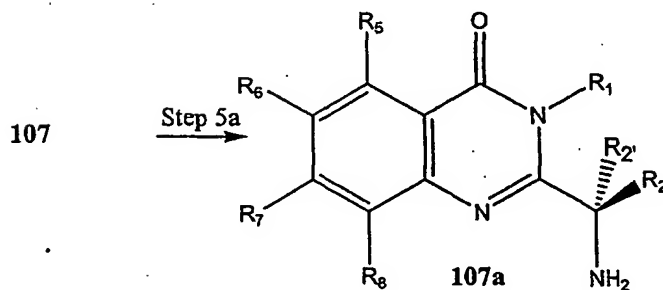
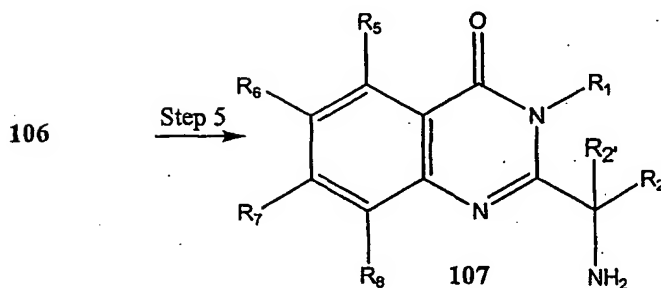
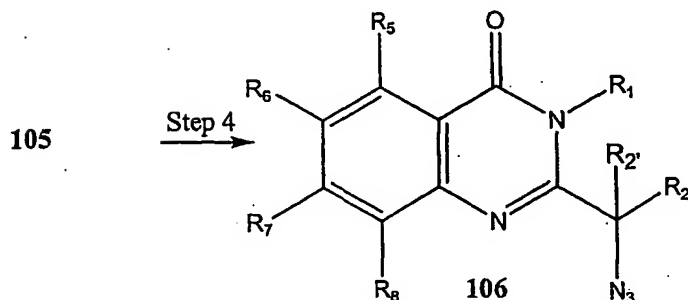
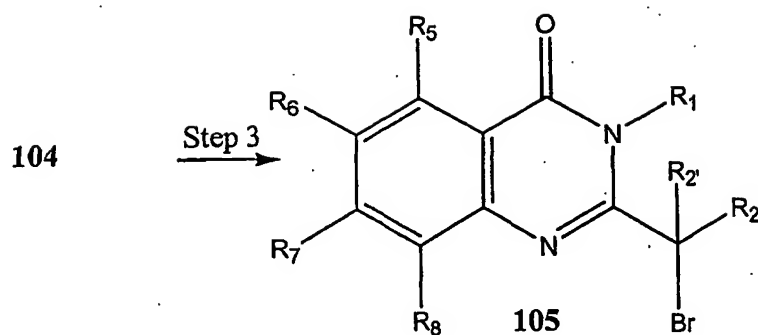
15 synthetic methodology.

Reaction Scheme 1



20





Preparation of Formula 103

Referring to Reaction Scheme 1, Step 1, to an optionally substituted benzoic acid (the compound of Formula 101) dissolved in an inert organic solvent (such as THF) in the presence of sodium bicarbonate and a dehydrating agent (such as Na_2SO_4) is added a slight molar excess of an optionally substituted acid chloride (the compound of Formula 102), maintaining about room temperature. Completion of the reaction is monitored, e.g., by TLC. Acetic anhydride is then added to the reaction

mixture, which is heated to about 90-100°C, monitoring completion of the reaction (e.g., by TLC) followed by removal of the acetic anhydride under vacuum at about 80-100°C. The reaction mixture is cooled and the corresponding, optionally substituted benzo[d][1,3]oxazin-4-one (the compound of Formula 103) is isolated and purified.

5

Preparation of Formula 104

Referring to Reaction Scheme 1, Step 2, about 1.5 molar equivalents of a primary amine (such as R_1NH_2) and 1 molar equivalent of a compound of Formula 103 in an inert organic solvent (such as toluene) are heated to reflux. The reaction takes place over a period of 1 to 5 hours. After removal of water, ethylene glycol and sodium hydroxide are added to the reaction mixture and the temperature raised to 110-120°C. Completion of the reaction is monitored, e.g., by TLC. The corresponding, optionally substituted quinazolinone (a compound of Formula 104) is isolated and purified.

15 Preparation of Formula 105

Referring to Reaction Scheme 1, Step 3, a compound of Formula 104, dissolved in acetic acid and in the presence of sodium acetate, is heated to about 30°C, followed by the addition (with agitation) of a slight molar excess of bromine in acetic acid over a period of 2.5 hours. Completion is monitored, e.g., by TLC; if the starting material continues to be present, temperature is increased to about 50°C until completion. The corresponding, optionally substituted quinazolinone of Formula 105 is isolated and purified.

20

Preparation of Formula 106

Referring to Reaction Scheme 1, Step 4, to 1.5 molar equivalents of sodium azide in an inert organic solvent (such as DMF) is slowly added 1 molar equivalent of a compound of Formula 105. The reaction takes place with agitation at a temperature of about 40°C over a period of 3 to 10 hours. Completion is monitored, e.g., by TLC. The corresponding, optionally substituted quinazolinone azide of Formula 106 is isolated and purified.

25

30 Preparation of Formula 107

Referring to Reaction Scheme 1, Step 5, to a solution of triphenylphosphine dissolved in an inert organic solvent (such as THF) is added an azide of Formula 106, portionwise over about 15 minutes. The reaction takes place with agitation,

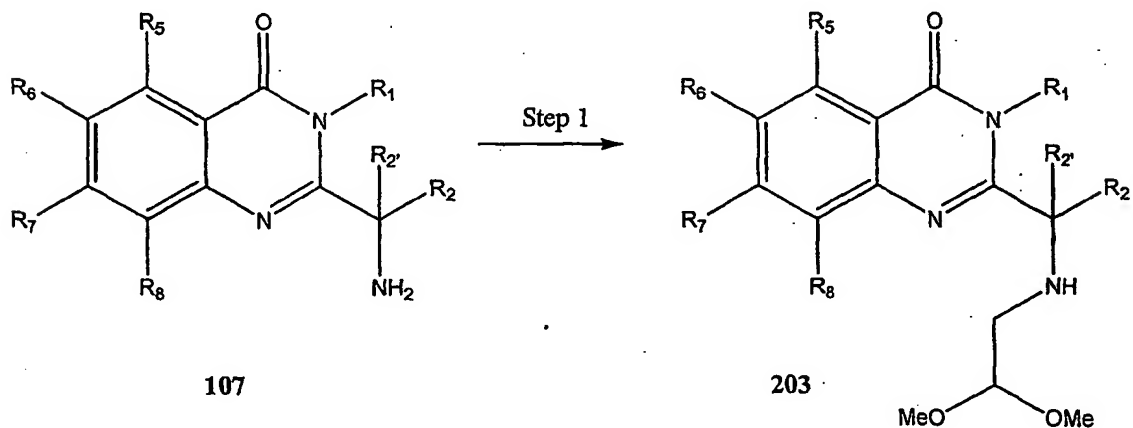
maintaining the temperature at 20°C over a period of 5 minutes to 1 hour. The reaction mixture is acidified, solvents removed followed by conventional work up to give the hydrochloride salt of the corresponding, optionally substituted quinazolinone of Formula 107, which is isolated and purified in the usual manner.

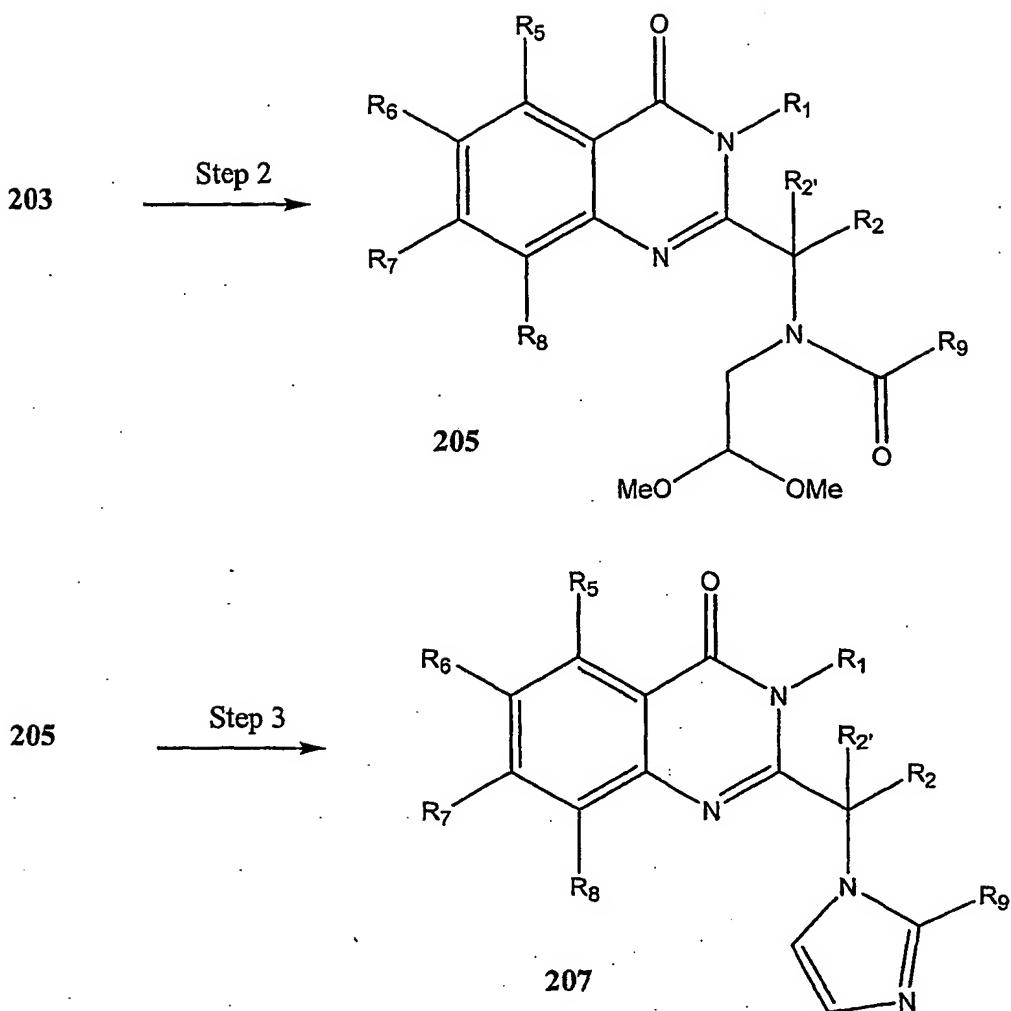
5 Preparation of Formula 107a

In certain compounds of the invention, particular stereoconfiguration can be preferred for the R₂ substituent, such as the (R) isomer, which can be obtained, e.g., as illustrated in optional Step 5a of Reaction Scheme 1. An amine of Formula 107 is dissolved in an inert organic solvent (such as IPA) and warmed to 60°C. In a separate vessel, a resolving agent (such as dibenzoyl-D-tartaric acid) is dissolved, preferably in the same warm solvent, and then quickly added (with agitation) to the warm amine solution. The reaction mixture is left to crystallize by cooling to room temperature over 16 hours under continuing agitation. The desired isomer, e.g., the (R) isomer illustrated as Formula 107a, is isolated and purified in the usual manner.

For the sake of brevity in the remaining description of the synthesis of compounds of Formula Ia or Ib, it should be understood that either single isomer or a mixture of isomers may be employed to give the corresponding product.

Reaction Scheme 2





Preparation of Formula 203

5 Referring to Reaction Scheme 2, Step 1, to an optionally substituted compound of Formula 107 dissolved in a polar, aprotic solvent (such as DMF) in the presence of a base (such as potassium carbonate) is added one equivalent of an optionally substituted suitably protected aldehyde having a halogen substituent. The solution is heated at reflux, monitoring completion of the reaction (e.g., by TLC). The reaction mixture is cooled and the corresponding, optionally substituted quinazolinone of Formula 203 is isolated and purified.

Preparation of Formula 205

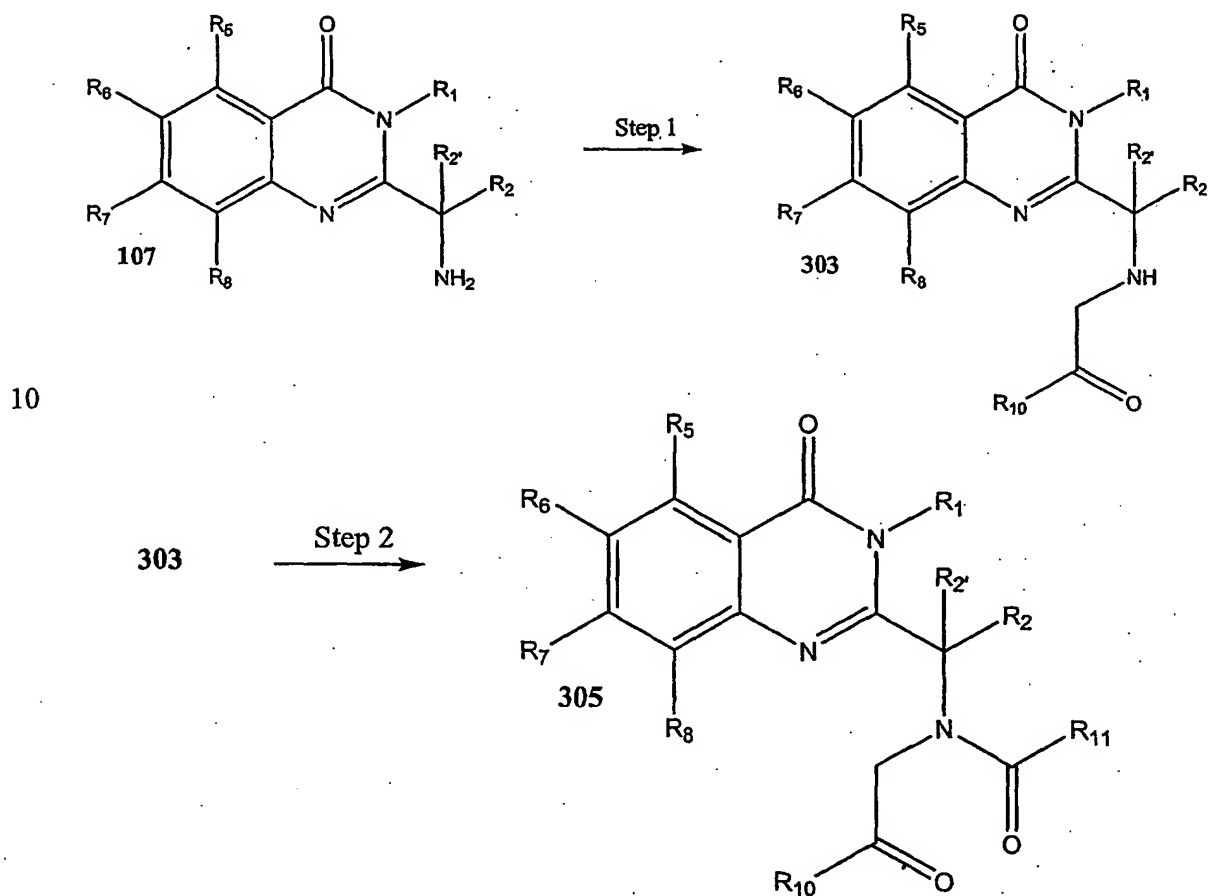
15 Referring to Reaction Scheme 2, Step 2, to an optionally substituted compound of Formula 203 in an inert solvent (such as dichloromethane) in the presence of about 1.5 molar equivalents of an amine base (such as triethylamine) is added about 1.5 molar equivalents of an R_9 acid chloride where R_9 is as described above. The reaction takes place, with stirring, at room temperature over a period of 4

to 24 hours. Completion is monitored, e.g., by TLC. The corresponding compound of Formula 205 is isolated and purified.

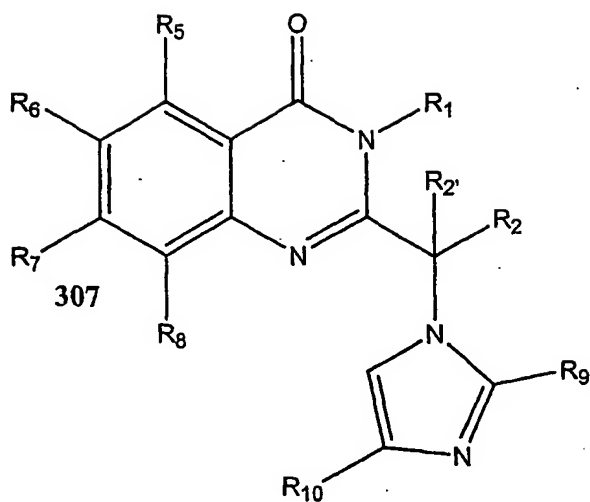
Preparation of Formula 207

- Referring to Reaction Scheme 2, Step 3, a solution of a compound of Formula 205 and an excess of ammonium acetate in acetic acid is heated at reflux for 1-4 hours. Completion is monitored, e.g., by TLC. The corresponding compound of Formula 207 is isolated and purified.

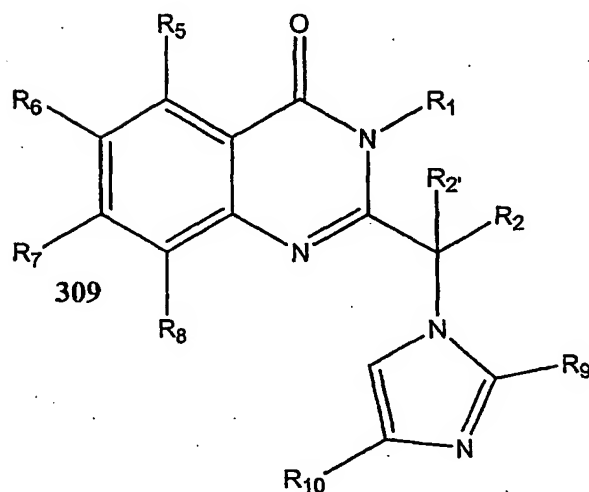
Reaction Scheme 3



305 $\xrightarrow{\text{Step 3}}$



307 $\xrightarrow{\text{Step 4}}$



Preparation of Formula 303

5 Referring to Reaction Scheme 3, Step 1, a suspension of a compound of Formula 107, an alpha-haloketone reagent of the Formula $R_{10}(CO)CH_2X$ wherein X is a leaving group, preferably, a halide, and about an equivalent of a base, such as potassium carbonate in a polar, aprotic solvent such as DMF is stirred at room temperature. The reaction is diluted with water and the resulting solid is used in the subsequent step without further purification.

10

Preparation of Formula 305

Referring to Reaction Scheme 3, Step 2, a solution of the compound from previous step, about an equivalent of an amine base, such as triethylamine and about an equivalent of an acid chloride (such as p-toluoyl chloride) in an organic solvent such as methylene chloride is stirred at room temperature for several hours.

15 Completion is monitored, e.g., by TLC. The corresponding compound of Formula

305 is isolated and purified.

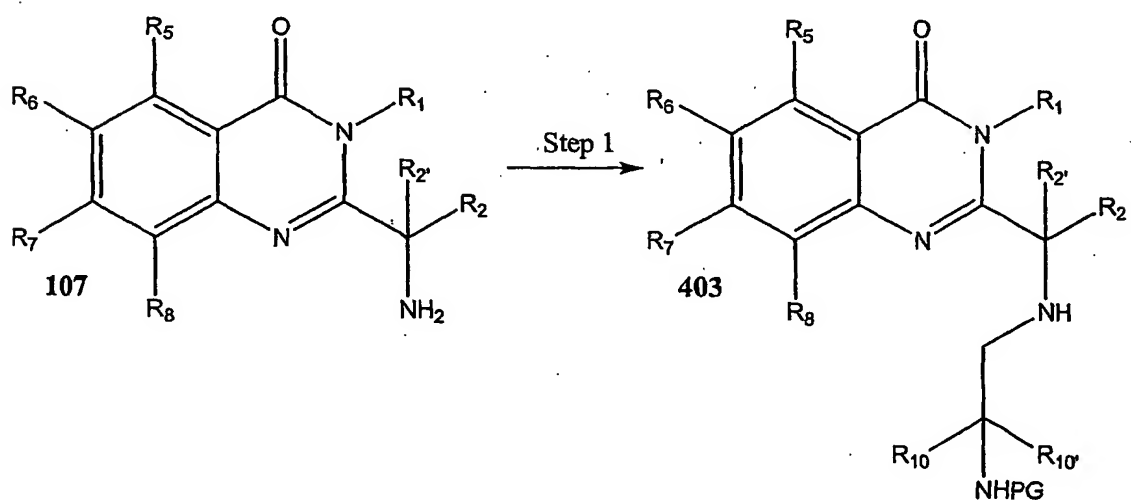
Preparation of Formula 307

Referring to Reaction Scheme 3, Step 3, a solution of a compound of Formula 305 and an excess of ammonium acetate in acetic acid is heated at reflux using a Dean-Stark trap and condenser. Completion is monitored, e.g., by TLC. The corresponding compound of Formula 307 is isolated and purified.

Preparation of Formula 309

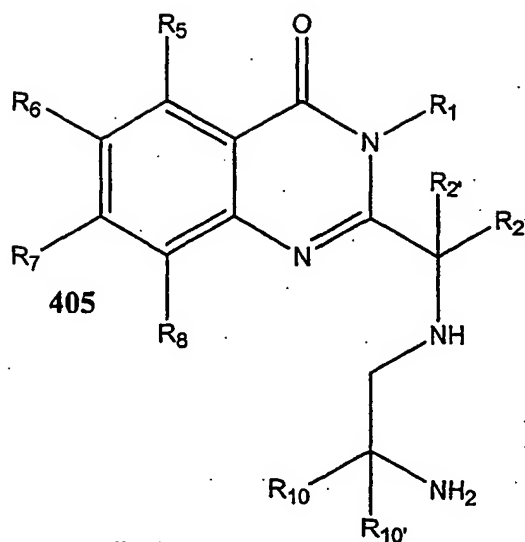
Optionally, in the event that group R_{10} comprises a functionality bearing a protecting group, the protecting group is removed. Thus, if R_{10} further comprises an amine bearing a Pht group, the protecting group is removed as shown in Reaction Scheme 3, Step 4. A solution of a compound of Formula 307 and an excess of anhydrous hydrazine in a polar, protic solvent such as ethanol is heated at reflux. The reaction is cooled to about 5°C and any precipitate is filtered off. The filtrate is concentrated in vacuo and purified to yield a compound of Formula 309.

Reaction Scheme 4



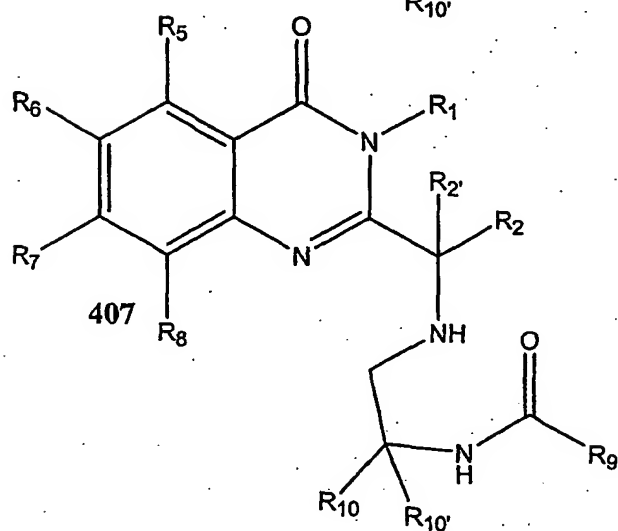
403

Step 2



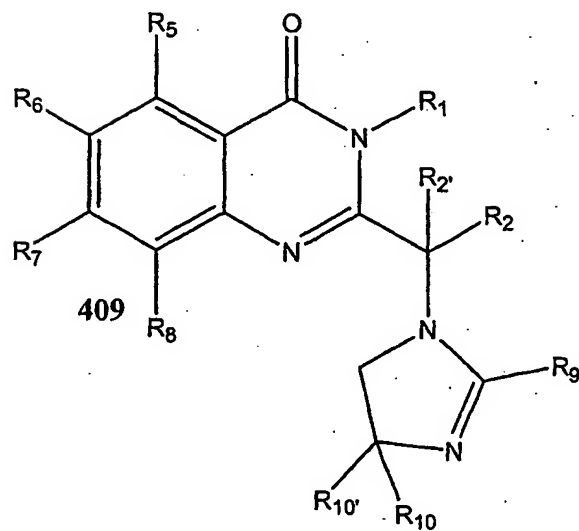
405

Step 3



407

Step 4



Preparation of Formula 403

Referring to Reaction Scheme 4, Step 1, reductive amination of amines of Formula 107 (prepared as described in WO 0130768) with an optionally substituted, aldehyde-containing carbamic acid ester (Seki *et. al. Chem. Pharm. Bull.* 1996, 44, 2061) gives urethane intermediates. Removal of the Boc-protecting group furnishes amines of Formula 405.

More specifically, to a solution of a compound of Formula 107 and an equivalent of a suitably protected aldehyde (Seki *et. al. Chem. Pharm. Bull.* 1996, 44, 2061) in dichloromethane is added a slight excess of a reducing agent, such as sodium triacetoxyborohydride. The resultant cloudy mixture is maintained at ambient temperature. Completion is monitored, e.g., by TLC. The corresponding compound of Formula 403 is isolated and used in the subsequent step without purification.

Preparation of Formula 405

Referring to Reaction Scheme 4, Step 2, the amine protecting group, PG, is then removed. For example, when PG is Boc, to a solution of a compound of Formula 403 in a polar, aprotic solvent such as dichloromethane is added a strong acid such as trifluoroacetic acid. The resultant solution is maintained at ambient temperature overnight and concentrated under reduced pressure. The residue is isolated and purified to give a compound of Formula 405 which was used in the subsequent step without purification.

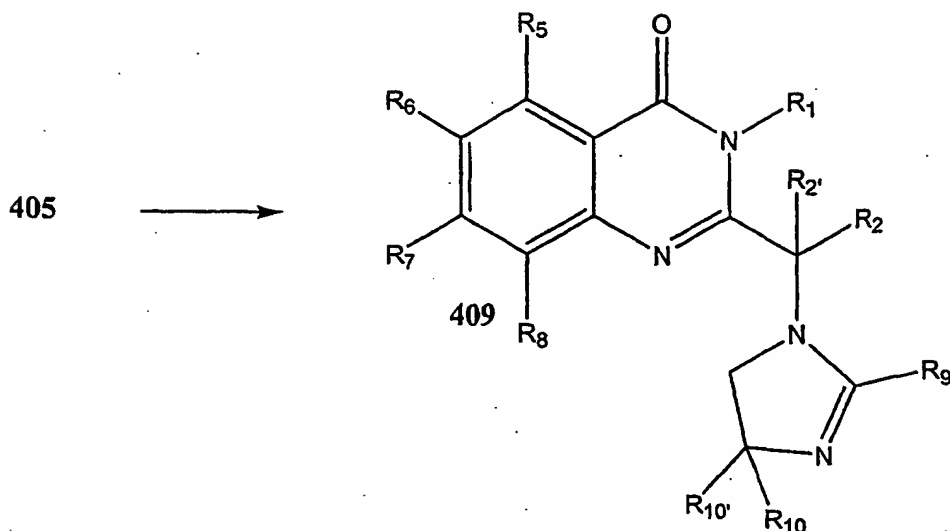
Preparation of Formula 407

Referring to Reaction Scheme 4, Step 3, to a solution of a compound of Formula 405 in a polar, aprotic solvent such as dichloromethane is added an excess, preferably about two equivalents of an amine base such as triethylamine, followed by about an equivalent or slight excess of an acid chloride. The resultant solution is stirred at ambient temperature for about 3 hours. Completion is monitored, e.g., by TLC. The corresponding compound of Formula 407 is isolated and purified.

Preparation of Formula 409

Referring to Reaction Scheme 4, Step 4, a solution of a compound of Formula 407 in an excess of phosphorus oxychloride is heated at reflux. After 8 hours, the reaction mixture is allowed to cool to ambient temperature and concentrated under reduced pressure. The corresponding compound of Formula 409 is isolated and purified.

Reaction Scheme 5

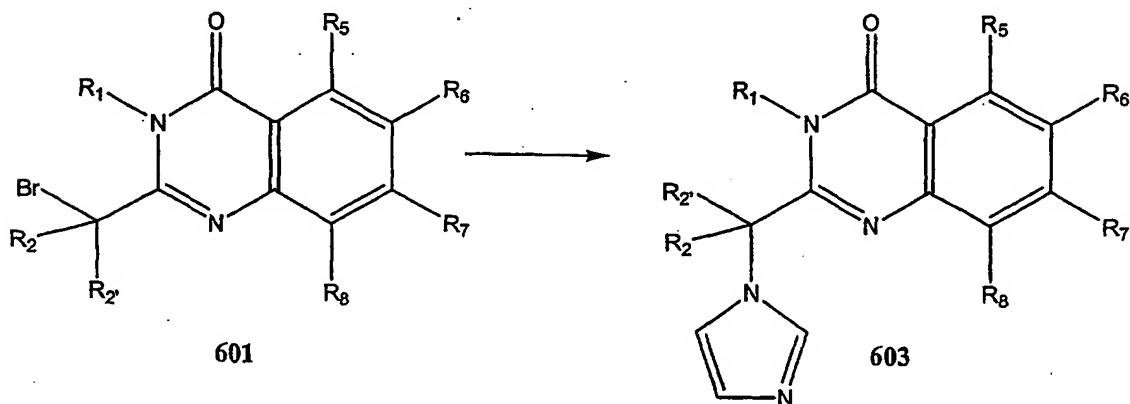


Preparation of Formula 409

As an alternative to Steps 3 and 4 of Reaction Scheme 4, acylation of primary amines of Formula 405, followed by acetic acid mediated cyclization, can proceed without isolation of the intermediate amides to provide the target compound of Formula 409. This route is shown in Reaction Scheme 5.

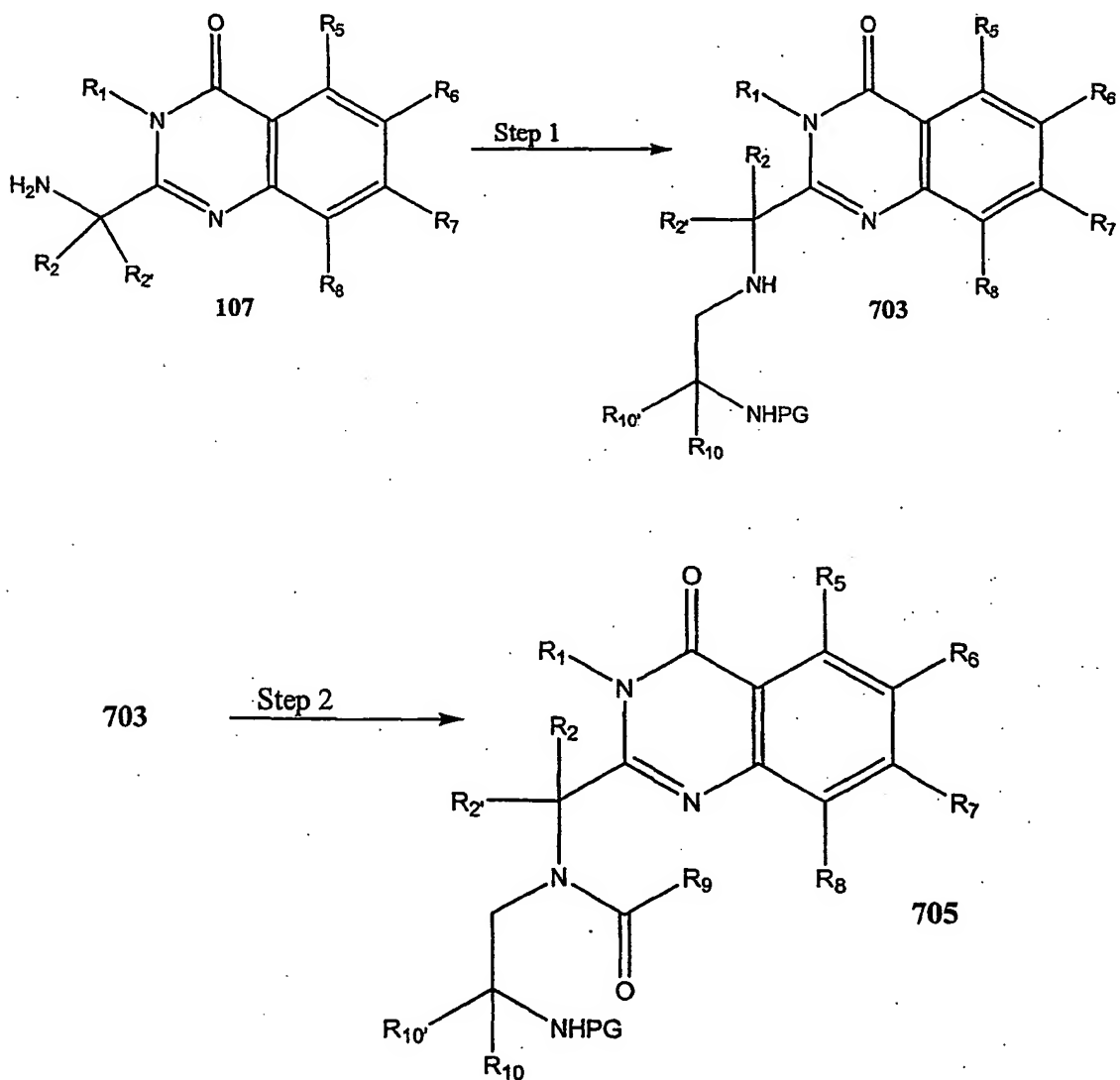
More specifically, to a solution of a compound of Formula 405 in a polar, aprotic solvent such as dichloromethane is added an excess, preferably about two equivalents of an amine base, such as triethylamine, followed by about an equivalent of an acid chloride. The resultant solution is stirred at ambient temperature for 2 hours, then evaporated under reduced pressure. The resultant solid is treated with glacial acetic acid, then the resultant suspension is heated at reflux for about 48 hours. The reaction is cooled to ambient temperature then evaporated under reduced pressure. The corresponding compound of Formula 409 is isolated and purified.

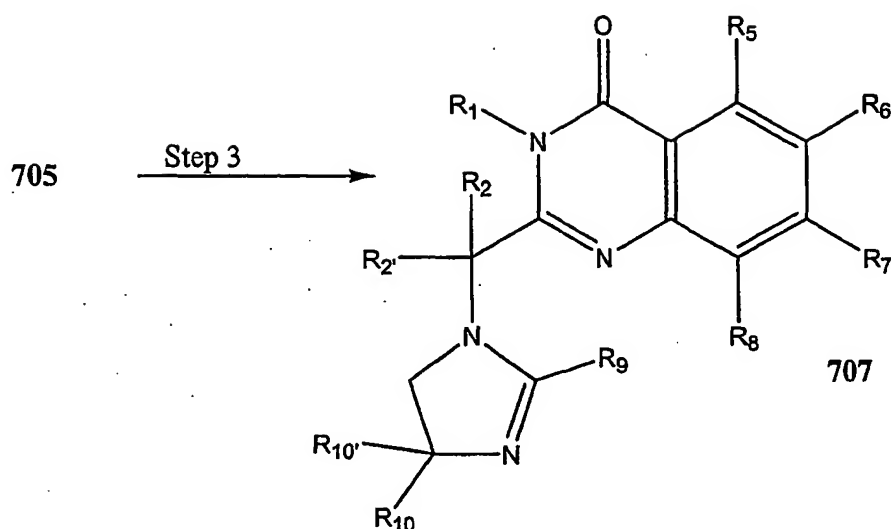
Reaction Scheme 6



Preparation of Compounds of Formula 603

Referring to Reaction Scheme 6, to a solution of a compound of Formula 601 in a nonpolar, aprotic solvent such as DMF are added a base such as triethylamine and an excess (preferably, about 1.5 equivalents) of imidazole followed by about an equivalent of tetrabutylammonium iodide. The resultant solution is heated to about 90 °C, stirred for about 18 h and allowed to cool to room temperature. The product, a compound of Formula 603, is isolated and purified.

Reaction Scheme 7



Preparation of Compounds of Formula 703

Referring to Reaction Scheme 7, Step 1, to a solution of a compound of Formula 107 and an excess of an optionally substituted, aldehyde-containing carbamic acid ester such as ((*S*)-4-benzyloxycarbonylamino-1-formyl-butyl)-carbamic acid *tert*-butyl ester) in a nonpolar, aprotic solvent such as CH₂Cl₂ is added sodium triacetoxyborohydride. The mixture is stirred overnight. The product, a compound of Formula 703, is isolated and purified.

Preparation of Compounds of Formula 705

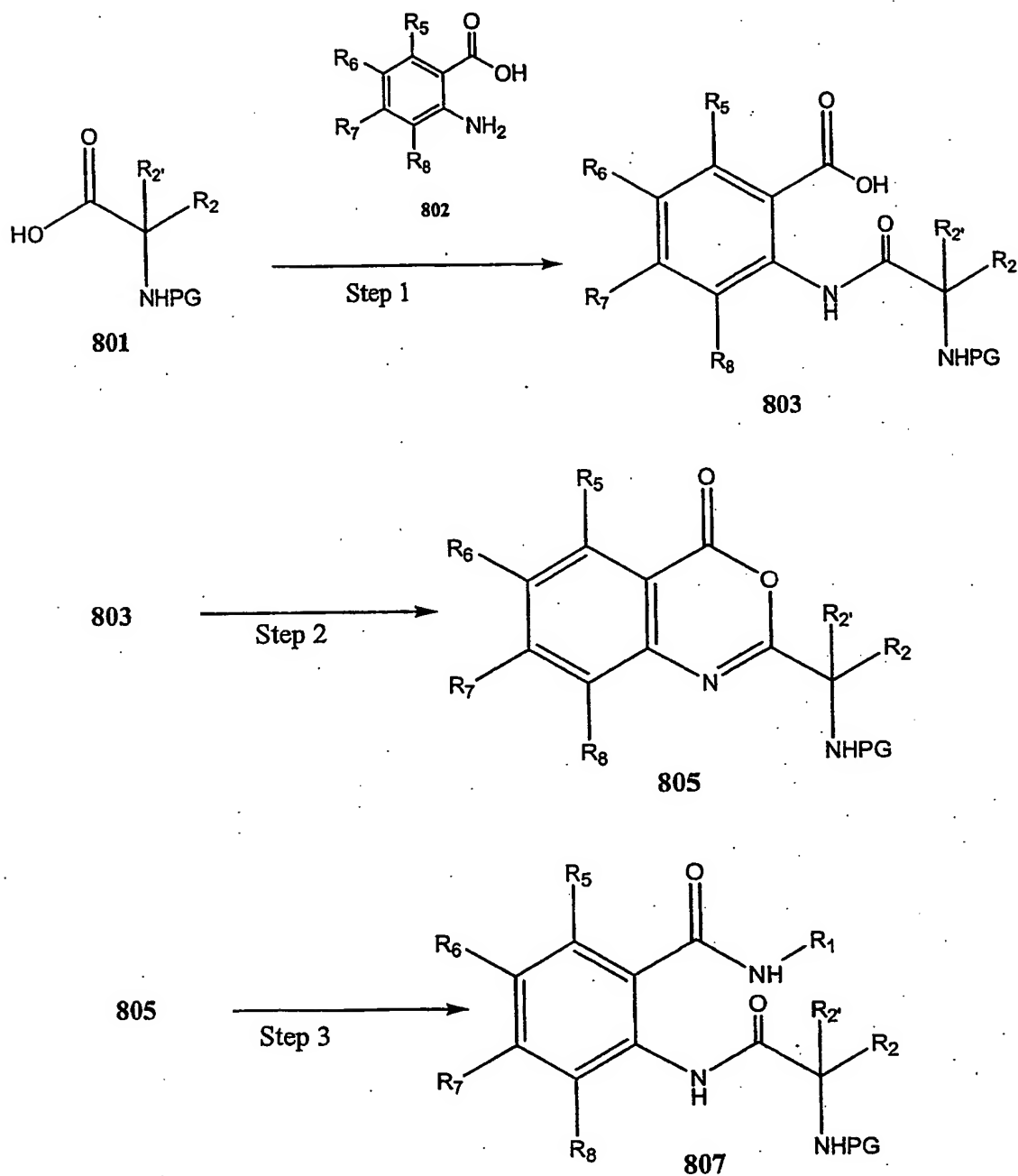
Referring to Reaction Scheme 7, Step 2, to a solution of a compound of Formula 703 in a nonpolar, aprotic solvent such as toluene is added a base such as triethylamine followed by dropwise addition of an excess of an acid chloride of the formula R₉-COCl. The reaction mixture is heated to about 80 °C for about 18 h, then at reflux for about 4 h. The product, a compound of Formula 705, is isolated and purified.

Preparation of Compounds of Formula 707

Referring to Reaction Scheme 7, Step 3, a solution of a compound of Formula 705 in a solvent such as CH₂Cl₂/TFA (preferably, about 4:1 CH₂Cl₂/TFA) is stirred at room temperature. The reaction mixture is concentrated under reduced pressure and the residue is diluted with a nonpolar, aprotic solvent such as CH₂Cl₂ and washed with aqueous base. The aqueous layer is extracted with a nonpolar, aprotic solvent such as CH₂Cl₂ and the combined extracts are dried, filtered and concentrated under reduced pressure. The residue is diluted with a nonpolar, aprotic solvent such as THF and aqueous base (preferably, saturated aqueous NaHCO₃). The mixture is stirred at room

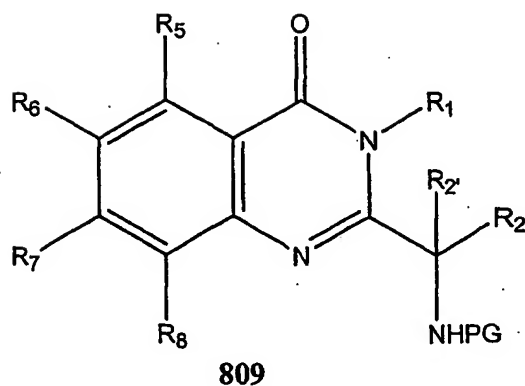
temperature for 10 days. The product, a compound of Formula 707, is isolated and purified.

Reaction Scheme 8



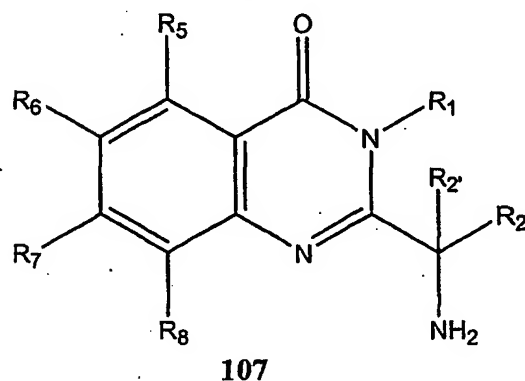
807

Step 4



809

Step 5



Preparation of Compounds of Formula 803

Referring to Reaction Scheme 8, Step 1, a compound of Formula 801 (e.g., an
 5 N-protected, chiral, naturally occurring or substituted amino acid such as valine;
 preferably *N*-Boc-*D*-valine) is converted to the corresponding compound of Formula
 803. Any naturally occurring and substituted α -amino acids can be employed as the
 compound of Formula 801, such as alanine, valine, leucine, isoleucine, phenylglycine,
 phenylalanine, serine, threonine, cysteine, methionine, tryptophan, tyrosine,
 10 asparagine, glutamine, asparaginate, glutamate, lysine, arginine, histidine and 2-
 aminobutyric acid; preferably alanine, valine, leucine, isoleucine, phenylglycine or 2-
 aminobutyric acid. Art-recognized N-protecting groups can be employed in the
 compound of Formula 801, including Boc, CBZ, phthalide, alloc, and teoc.

The compound of Formula 801 is dissolved in an organic solvent (such as
 15 THF) in the presence of 1 to 2 molar equivalents of a base (such as *N*-
 methylmorpholine) and cooled to 0°C. Approximately 1 to 2 molar equivalents of
 isobutyl chloroformate is slowly added preferably with stirring. The mixture is
 maintained at 0°C and stirred for 1 to 2 hours (preferably 1.5 hours) to give the
 corresponding mixed anhydride (not shown). The mixed anhydride is carried forward
 20 without isolation or purification by the addition in one portion of an equimolar

amount of an optionally substituted anthranilic acid of Formula 802 followed by the addition of a second equimolar amount of the base (such as *N*-methylmorpholine). The reaction takes place at 0°C over a period of 1 to 5 hours to give the corresponding compound of Formula 803 (which can also be carried forward without isolation or purification).

Preparation of Compounds of Formula 805

Referring to Reaction Scheme 8, Step 2, a compound of Formula 803 is converted to the corresponding compound of Formula 805. An additional 1 to 2 molar equivalents of isobutyl chloroformate is added to a compound of Formula 803 along with the addition of 1 to 2 molar equivalents of a base (such as *N*-methylmorpholine). The reaction takes place at 0°C over a period of 1 to 3 hours to give the corresponding compound of Formula 805 (which can also be carried forward without isolation or purification).

Preparation of Compounds of Formula 807 and 809

Referring to Reaction Scheme 1, Step 3, a compound of Formula 805 is converted to the corresponding compounds of Formula 807 and 809. One to 3 molar equivalents of an amine of Formula R_1NH_2 are added with continued stirring to a compound of Formula 805. The reaction takes place at 0°C to the corresponding compounds of Formula 807 and Formula 809, each of which can be isolated and purified.

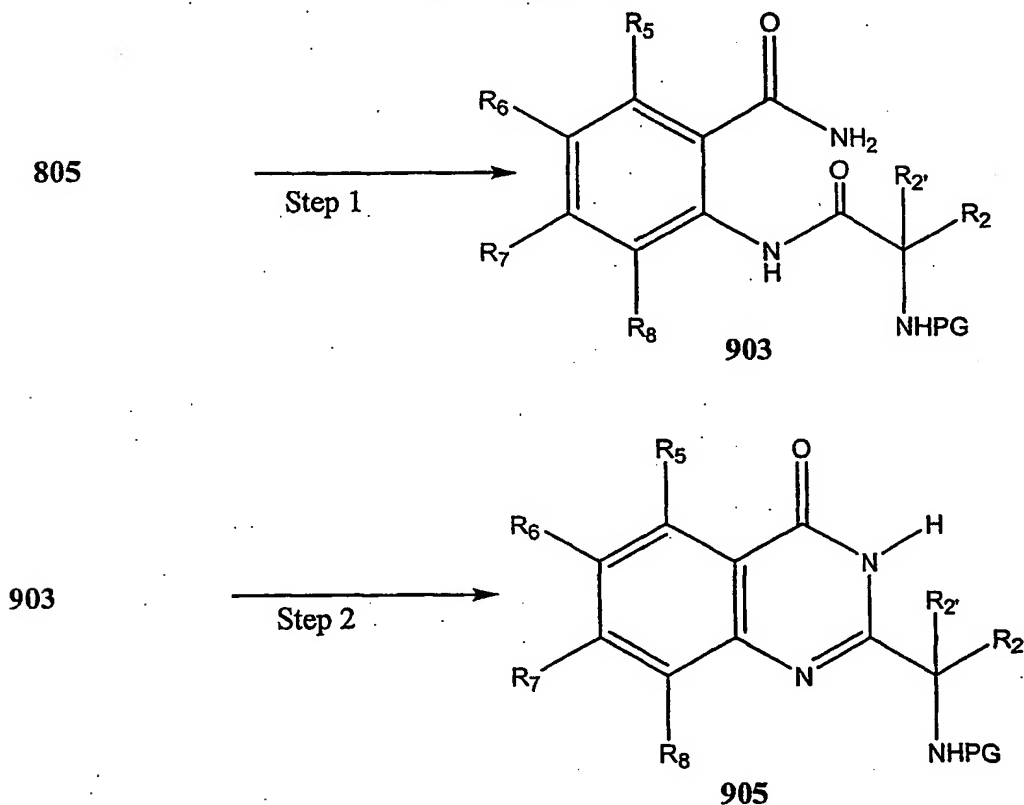
Preparation of Compounds of Formula 809

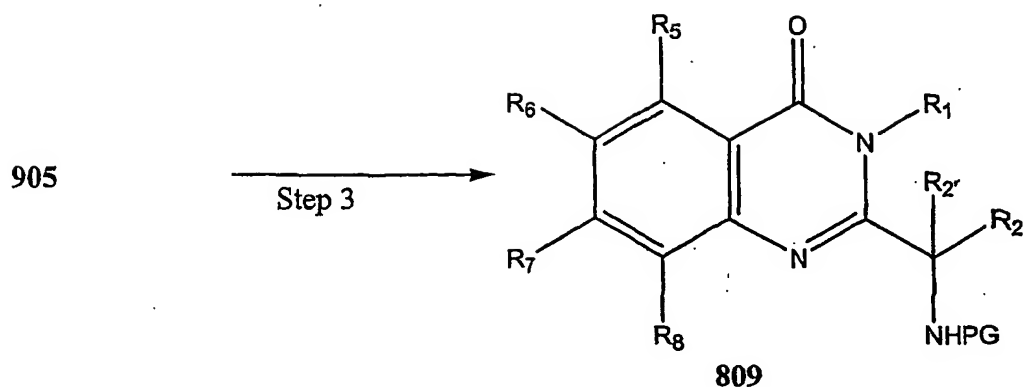
Referring to Reaction Scheme 1, Step 4, a compound of Formula 807 is converted to the corresponding quinazolinone of Formula 809. A compound of Formula 807 is dissolved in an organic solvent (e.g., 1,4-dioxane/ethylene glycol 2:1 or dimethoxyethane), contacted with a slight to twice molar excess of a cyclo-dehydration reagent (e.g., lithium hydroxide monohydrate, HMDS, phosphorous oxychloride, oxalyl chloride, thionyl chloride, Burgess' reagent, Ph_3P/I_2 , or a Vilsmeier reagent (DMF with phosphorous oxychloride, or DMF with thionyl chloride), preferably HMDS) and heated to reflux. The reaction takes place at reflux over a period of 3 to 36 hours, followed by cooling and optionally acidification of the mixture to give a suspension of the corresponding quinazolinone of Formula 809, which is then isolated and purified by conventional procedures. Reaction time and work-up will depend on the cyclo-dehydration reagent that is employed.

Preparation of Compounds of Formula 107

Referring to Reaction Scheme 8, Step 7, the amino protecting group of a compound of Formula 809 is removed. For example, to a solution of a compound of Formula 809 wherein the amino protecting group, PG, is Boc in a polar, aprotic solvent such as dichloromethane is added trifluoroacetic acid, while maintaining the temperature at about 0°C. The resulting solution is then stirred at room temperature for one hour and concentrated *in vacuo*. The product, a compound of Formula 107, is isolated and used in the next step without further purification. One of skill in the art will readily appreciate that the removal of other protecting groups can be accomplished using conditions known in the art. See, e.g., Greene, et al. *supra*.

Reaction Scheme 9





Preparation of Compounds of Formula 903

Referring to Reaction Scheme 9, Step 1, a compound of Formula 805 is converted to the corresponding carbamide of Formula 903. Gaseous ammonia is bubbled through a solution of the compound of Formula 805. The reaction takes place with stirring at 0°C over a period of 1 to 3 hours followed by isolation and purification via conventional procedures.

Preparation of Compounds of Formula 905

Referring to Reaction Scheme 9, Step 2, a compound of Formula 903 is converted to the corresponding quinazolinone of Formula 905. The compound of Formula 903 is dissolved in an organic solvent (preferably THF) and contacted with a slight molar excess of a strong base (preferably lithium hydroxide monohydrate) to give the corresponding compound of Formula 905. The reaction takes place at reflux over a period of about 30 minutes to 2 hours, followed by cooling and acidification of the mixture to give a suspension, which is then isolated and purified via conventional procedures.

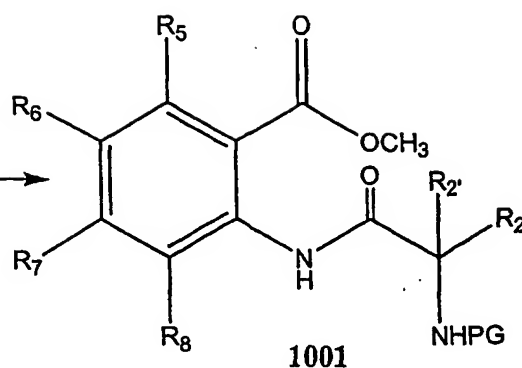
Preparation of Compounds of Formula 809

Referring to Reaction Scheme 9, Step 3, a compound of Formula 905 is converted to the corresponding 3-*N*-substituted quinazolinone of Formula 809. The compound of Formula 807 is dissolved in an organic solvent (e.g., DMF) and *N*-substituted via contact with a compound of Formula R₁X wherein X is a leaving group (preferably a halide or tosylate) in the presence of an alkaline metal carbonate or hydride. The reaction takes place at room temperature over a period of 10 to 20 hours to give the corresponding compound of Formula 809, which is isolated and purified.

Reaction Scheme 10

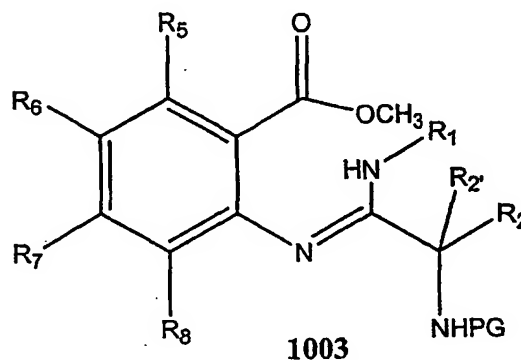
805

Step 1



1001

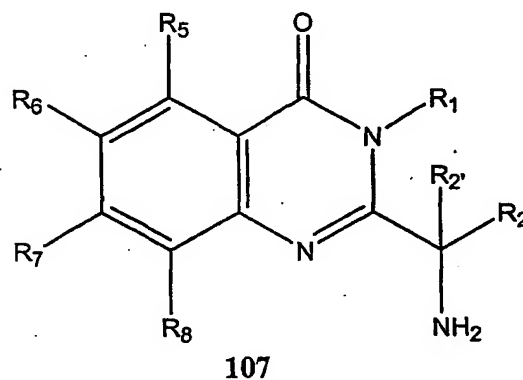
Step 2



5

1003

Step 3



Preparation of Compounds of Formula 1001

Referring to Reaction Scheme 10, Step 1, a compound of Formula 805 is opened with methanol and converted to the corresponding ester of Formula 1001. The compound of Formula 1001 is isolated and optionally purified.

Preparation of Compounds of Formula 1003

Referring to Reaction Scheme 10, Step 2, an ester of Formula 1001 is converted to the corresponding amidine of Formula 1003.

15 Preparation of Compounds of Formula 107

Referring to Reaction Scheme 10, Step 3, an amidine of Formula 1003 is cyclized to afford the corresponding compound of Formula 107.

Preferred Processes and Last Steps

A compound of Formula Ia or Ib is optionally contacted with a
5 pharmaceutically acceptable acid or base to form the corresponding acid or base addition salt.

A pharmaceutically acceptable acid addition salt of a compound of Formula Ia or Ib is optionally contacted with a base to form the corresponding free base of Formula Ia or Ib.

10 A pharmaceutically acceptable base addition salt of a compound of Formula Ia or Ib is optionally contacted with an acid to form the corresponding free acid of Formula Ia or Ib.

Particular Embodiments of Compounds of the Invention

R₁

15 When considering the compounds of Formula Ia or Ib, in one embodiment, R₁ is selected from hydrogen, optionally substituted C₁-C₈ alkyl-, optionally substituted aryl-, optionally substituted heteroaryl-, optionally substituted aryl-C₁-C₄-alkyl-, and optionally substituted heteroaryl-C₁-C₄-alkyl- (more preferably optionally substituted aryl- and optionally substituted aryl-C₁-C₄-alkyl-). In a more particular embodiment
20 R₁ is selected from hydrogen, optionally substituted C₁-C₄ alkyl-, optionally substituted phenyl-C₁-C₄-alkyl-, optionally substituted naphthalenylmethyl-, optionally substituted phenyl-, and naphthyl-. Even more particularly, R₁ is optionally substituted phenyl-C₁-C₄-alkyl-, optionally substituted heteroaryl-C₁-C₄-alkyl-, or naphthalenylmethyl-. Yet more particularly, R₁ is benzyl-, cyanobenzyl-,
25 methoxybenzyl-, or naphthalenylmethyl-. Most particularly, R₁ is benzyl-.

R₂ and R₂'

When considering the compounds of Formula Ia or Ib, and as will be appreciated by those skilled in the art, the compounds described herein possess a potentially chiral center at the carbon to which R₂ and R₂' are attached. The R₂ and R₂'
30 groups may be the same or different; if different, the compound is chiral (i.e., has a stereogenic center). When R₂ and R₂' are different, in particular embodiments R₂' is hydrogen and R₂ is other than hydrogen. The invention contemplates the use of pure enantiomers and mixtures of enantiomers, including racemic mixtures, although the

use of a substantially optically pure enantiomer will generally be preferred. The term "substantially pure" means having at least about 95% chemical purity with no single impurity greater than about 1%. The term "substantially optically pure" or "enantiomerically pure" means having at least about 97.5% enantiomeric excess. In a particular embodiment, the stereogenic center to which R_2 and $R_{2'}$ are attached is of the R configuration.

When considering the compounds of Formula Ia or Ib, R_2 and $R_{2'}$ are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaralkyl-.

In one embodiment, R_2 and $R_{2'}$ taken together form a 3- to 7-membered ring which may optionally be substituted one or more of the following groups: hydroxyl, halogen (particularly chloro and fluoro), optionally substituted C_1 - C_4 alkyl- (particularly methyl-), C_1 - C_4 alkoxy (particularly methoxy), cyano substituted amino, or carbamyl-.

In one embodiment, R_2 is optionally substituted C_1 - C_4 alkyl-, and $R_{2'}$ is hydrogen or optionally substituted C_1 - C_4 alkyl-. More suitably, $R_{2'}$ is hydrogen and R_2 is optionally substituted C_1 - C_4 alkyl-. In a most particular embodiment R_2 is chosen from methyl-, ethyl-, propyl- (particularly, *c*-propyl- or *i*-propyl-), butyl- (particularly, *t*-butyl-), methylthioethyl-, methylthiomethyl-, aminobutyl-, (CBZ)aminobutyl-, cyclohexylmethyl-, benzyloxymethyl-, methylsulfanylethyl-, methylsulfanylmethyl-, and hydroxymethyl-, and $R_{2'}$ is hydrogen. Especially chosen embodiments are when $R_{2'}$ is hydrogen and R_2 is ethyl- or propyl- (particularly, *c*-propyl- or *i*-propyl-). Even more particularly, R_2 is *i*-propyl-. Yet more particularly, the stereogenic center to which R_2 and $R_{2'}$ is attached is of the R configuration.

In one embodiment, if either R_2 or $R_{2'}$ is hydrogen, then the other is not hydrogen. In another embodiment, both R_2 and $R_{2'}$ are hydrogen.

R_5 , R_6 , R_7 , and R_8

In other embodiments R_5 , R_6 , R_7 , and R_8 are independently chosen from hydrogen, hydroxyl, halogen (particularly chloro and fluoro), optionally substituted C_1 - C_4 alkyl- (particularly methyl-), C_1 - C_4 alkoxy (particularly methoxy), cyano substituted amino, or carbamyl-. More particularly, R_5 , R_6 , R_7 , and R_8 are methoxy, hydrogen or halo. For each of the specific substituents: R_5 is hydrogen or halo; R_6 is

hydrogen, optionally substituted C₁-C₄ alkyl- (particularly, methyl-) or halo; R₇ is hydrogen, halo, optionally substituted C₁-C₄ alkyl- (particularly, methyl- or trifluoromethyl-), C₁-C₄ alkoxy (particularly, methoxy), cyano, substituted amino, or carbamyl-; and R₈ is hydrogen, C₁-C₄ alkyl- (particularly, methyl-), C₁-C₄ alkoxy (particularly, methoxy), hydroxy, or halo. Still more particularly are the compounds where only one of R₅, R₆, R₇, and R₈ is not hydrogen, especially R₇. Another particular embodiment is drawn to the compounds where R₇ and R₈ are not hydrogen.

R₉

In a particular embodiment, R₉ is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, and optionally substituted heteroaryl-.

More particularly, R⁹ is hydrogen; optionally substituted lower-alkyl- (especially, methyloxymethyl-, aminoethyl-, methyl-, ethyl-, or propyl-); aryl- (especially phenyl-); substituted aryl- (especially phenyl- substituted with one or more of the following: optionally substituted lower-alkyl- (especially, methyl-, ethyl-, methoxymethyl-, or trifluoromethyl-), lower-alkoxy (especially, methoxy or methylenedioxy-), halo, aminocarbonyl-, or cyano); aralkyl- (especially benzyl- or phenylvinyl-); heteroaryl- (especially furyl-, thiophenyl-, pyridinyl-, isoxazolyl-, or quinoxalinyl-); substituted heteroaryl- (especially furyl-, thiophenyl-, pyridinyl-, quinoxalinyl-, or isoxazolyl- substituted with one or more of the following optionally substituted lower-alkyl- (especially, methyl-, methoxymethyl-, or trifluoromethyl-), halo, lower-alkoxy-, or cyano); or substituted aralkyl- (especially substituted benzyl- or substituted styrenyl-).

Yet more particularly, R₉ is hydrogen; methyl-; ethyl-; propyl-; phenyl-; tolyl-; ethylphenyl-; halophenyl-; acetaminophenyl-; cyanophenyl-; halomethylphenyl-; polyhalophenyl-; methyloxymethyl-; methoxyethyl-; methoxyphenyl-; dimethoxyphenyl-; methylenedioxyphenyl-; trifluoromethylphenyl-; furyl-; thiophenyl-; pyridinyl-; halomethylpyridinyl-; isoxazolyl-; methylisoxazolyl-; dimethylaminophenyl-; diethylaminophenyl-; isopropylphenyl-; or quinoxalinyl-.

R₁₀, R_{10'}, R₁₁, and R_{11'}

When considering compounds of Formula Ia or Ib, in a particular embodiment, R_{10} , $R_{10'}$, R_{11} , and $R_{11'}$ are independently selected from the group consisting of hydrogen, optionally substituted alkyl-, optionally substituted aryl-, and optionally substituted aralkyl-.

- 5 More particularly, R_{10} and $R_{10'}$ are independently selected from the group consisting of hydrogen; hydroxymethyl-; aminomethyl-; acetaminomethyl-; (carboxymethyl-amino)-methyl-; aminoethyl-; acetaminomethyl-; (carboxymethyl-amino)-ethyl-; hydroxyethyl-; aminopropyl-; acetaminopropyl-; (carboxymethyl-amino)-propyl-; hydroxypropyl-; methyl-; ethyl-; and propyl-.
- 10 In a particular embodiment, R_{11} and $R_{11'}$ are independently selected from the group consisting of hydrogen and optionally substituted lower-alkyl-. More particularly, R_{11} and $R_{11'}$ are hydrogen.

Particular Subgenus

- In a particular subgenus of Formula Ia, R_1 is benzyl-, halobenzyl-, methoxybenzyl-, cyanobenzyl-, or naphthylmethyl-; R_2 is chosen from ethyl- and propyl-; R_2' is hydrogen; R_5 is hydrogen; R_6 is hydrogen; R_7 is halo; R_8 is hydrogen; and R_9 is substituted phenyl-; R_{10} is methyl-, hydrogen, or amino lower-alkyl- (aminomethyl-, aminoethyl-, aminopropyl-); and R_{11} is hydrogen.
- 15

- In a particular subgenus of Formula Ib, R_1 is benzyl-, halobenzyl-, methoxybenzyl-, cyanobenzyl-, or naphthylmethyl-; R_2 is chosen from ethyl- and propyl-; R_2' is hydrogen; R_5 is hydrogen; R_6 is hydrogen; R_7 is halo; R_8 is hydrogen; and R_9 is substituted phenyl-; R_{10} and $R_{10'}$ are methyl-, hydrogen, or amino lower-alkyl- (aminomethyl-, aminoethyl-, aminopropyl-); and R_{11} and $R_{11'}$ are hydrogen.
- 20

- In a particular subgenus of Formula Ia, R_1 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aryl- C_1 - C_4 -alkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaryl- C_1 - C_4 -alkyl-;
- 25

- R_2 and R_2' are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aryl- C_1 - C_4 -alkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaryl- C_1 - C_4 -alkyl-; or R_2 and R_2' taken together form an optionally substituted 3- to 7-membered ring;
- 30

R_5 , R_6 , R_7 and R_8 are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted alkoxy, halogen, hydroxyl-, nitro,

cyano, dialkylamino, alkylsulfonyl-, alkylsulfonamido, alkylthio, carboxyalkyl-, carboxamido, aminocarbonyl-, optionally substituted aryl-, optionally substituted aryloxy, optionally substituted heteroaryl-, and optionally substituted heteroaryloxy;

5 R_9 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, and optionally substituted heteroaryl-; and

R_{10} , $R_{10'}$, R_{11} , and $R_{11'}$ are independently hydrogen, optionally substituted alkyl-, optionally substituted aryl-, or optionally substituted aralkyl,

10 provided that R_1 is not substituted phenyl when R_2 is methyl and R_2' is hydrogen.

Particular Compounds

Particular compounds include:

- 3-Benzyl-7-chloro-2-{1-[2-(4-chloro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3*H*-quinazolin-4-one;
- 15 3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3*H*-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(4-methoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3*H*-quinazolin-4-one;
- 20 3-Benzyl-7-chloro-2-{1-[4,4-dimethyl-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3*H*-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-thiophen-2-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(2-furan-2-yl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one;
- 25 3-Benzyl-7-chloro-2-[1-(2-methoxymethyl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-*m*-tolyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one;
- 30 3-Benzyl-7-chloro-2-{1-[2-(3-chloro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3*H*-quinazolin-4-one;
- Benzyl-7-chloro-2-[(*R*)-1-(4,4-dimethyl-2-*p*-tolyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3*H*-quinazolin-4-one;

- 3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-phenyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one trifluoroacetate;
- 5 3-Benzyl-7-chloro-2-{1-[2-(3,4-dichloro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(3,4-dimethoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 2-[1-(2-Benzo[1,3]dioxol-5-yl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 10 3-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-benzonitrile;
- 3-Benzyl-7-chloro-2-{1-[2-(2-chloro-6-methyl-pyridin-4-yl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 15 3-Benzyl-7-chloro-2-{1-[4,4-dimethyl-2-(5-methyl-isoxazol-3-yl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-3-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(3,5-dimethoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 20 3-Benzyl-7-chloro-2-{1-[2-(2,3-difluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(3-dimethylamino-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 25 3-Benzyl-7-chloro-2-{1-[2-(4-dimethylamino-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(4-isopropyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(3-chloro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 30 3-Benzyl-2-{1-[2-(3-bromo-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;

- 4- {1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-benzonitrile;
- 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-(2-tolyl)-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- 5 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-pyridin-3-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-pyridin-4-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 10 3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[(S)-2-(3-fluoro-4-methyl-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 15 3-Benzyl-7-chloro-2-[2-methyl-1-((S)-4-methyl-2-*p*-tolyl-4,5-dihydro-imidazol-1-yl)-propyl]-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(2-methoxy-ethyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[1-(2-isopropyl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- 20 3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-quinoxalin-2-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(4-ethyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 25 3-Benzyl-7-chloro-2-[(R)-2-methyl-1-(2-*p*-tolyl-4,5-dihydro-imidazol-1-yl)-propyl]-3H-quinazolin-4-one;
- N-(4-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-phenyl)-acetamide;
- 3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 30 3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3H-quinazolin-4-one;

- 3-Benzyl-7-chloro-2-((R)-1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl)-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[2-methyl-1-(2-phenyl-imidazol-1-yl)-propyl]-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[2-methyl-1-(2-p-tolyl-imidazol-1-yl)-propyl]-3H-quinazolin-4-one;
- 5 3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-phenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 4-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-1H-imidazol-2-yl}-benzonitrile;
- 3-Benzyl-7-chloro-2-{1-[2-(4-chloro-phenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4
- 10 one;
- 3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 15 3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-{1-[2-(methoxymethyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one;
- 2-(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione;
- 20 1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione;
- 2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one;
- (2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethylamino)-acetic acid tert-butyl ester;
- 25 (2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethylamino)-acetic acid;
- 2-{1-[4-(3-Amino-propyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-(1-imidazol-1-yl-2-methyl-propyl)-3H-quinazolin-4-one;
- 30 2-[(R)-1-(4-Aminomethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 2-[(R)-1-[4-Aminomethyl-2-(3-fluoro-4-methyl-benzoyl)-imidazol-1-yl]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one;

- N-{1-[(R)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-acetamide;
- 2-[(R)-1-[4-(N,N-Dicarboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 5 2-[(R)-1-[4-(N-Carboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one;
- 3-Benzyl-7-chloro-2-[(R)-1-(4-hydroxymethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one;
- (3-[(S)-1-[(R)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-4,5-dihydro-1H-imidazol-4-yl]-propyl)-carbamic acid benzyl ester; and
- 10 2-[(R)-1-[(S)-4-(3-Amino-propyl)-2-p-tolyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one.

Utility, Testing and Administration

General Utility

- 15 Once made, the compounds of the invention find use in a variety of applications involving alteration of mitosis. As will be appreciated by those skilled in the art, mitosis may be altered in a variety of ways; that is, one can affect mitosis either by increasing or decreasing the activity of a component in the mitotic pathway. Stated differently, mitosis may be affected (e.g., disrupted) by disturbing equilibrium,
- 20 either by inhibiting or activating certain components. Similar approaches may be used to alter meiosis.

- In a particular embodiment, the compounds of the invention are used to inhibit mitotic spindle formation, thus causing prolonged cell cycle arrest in mitosis. By "inhibit" in this context is meant decreasing or interfering with mitotic spindle
- 25 formation or causing mitotic spindle dysfunction. By "mitotic spindle formation" herein is meant organization of microtubules into bipolar structures by mitotic kinesins. By "mitotic spindle dysfunction" herein is meant mitotic arrest and monopolar spindle formation.

- The compounds of the invention are useful to bind to, and/or inhibit the
- 30 activity of, a mitotic kinesin, KSP. In one embodiment, the KSP is human KSP, although the compounds may be used to bind to or inhibit the activity of KSP kinesins from other organisms. In this context, "inhibit" means either increasing or decreasing spindle pole separation, causing malformation, i.e., splaying, of mitotic spindle poles,

or otherwise causing morphological perturbation of the mitotic spindle. Also included within the definition of KSP for these purposes are variants and/or fragments of KSP.

See U.S. Patent 6,437,115, hereby incorporated by reference in its entirety. The compounds of the invention have been shown to have specificity for KSP. However,
5 the present invention includes the use of the compounds to bind to or modulate other mitotic kinesins.

The compounds of the invention are used to treat cellular proliferation diseases. Such disease states which can be treated by the compounds, compositions and methods provided herein include, but are not limited to, cancer (further discussed
10 below), autoimmune disease, fungal disorders, arthritis, graft rejection, inflammatory bowel disease, cellular proliferation induced after medical procedures, including, but not limited to, surgery, angioplasty, and the like. Treatment includes inhibiting cellular proliferation. It is appreciated that in some cases the cells may not be in an abnormal state and still require treatment. Thus, in one embodiment, the invention
15 herein includes application to cells or individuals afflicted or subject to impending affliction with any one of these disorders or states.

The compounds, compositions and methods provided herein are particularly deemed useful for the treatment of cancer including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that
20 may be treated by the compounds, compositions and methods of the invention include, but are not limited to: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma,
25 bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors,
30 Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell

carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochondroma (osteochondrogenous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-theca cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above identified conditions.

30 Testing

For assay of KSP-modulating activity, generally either KSP or a compound according to the invention is non-diffusably bound to an insoluble support having isolated sample receiving areas (e.g., a microtiter plate, an array, etc.). The insoluble

support may be made of any composition to which the sample can be bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports may be solid or porous and of any convenient shape. Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharides, nylon or nitrocellulose, Teflon™, etc. Microtiter plates and arrays are especially convenient because a large number of assays can be carried out simultaneously, using small amounts of reagents and samples. The particular manner of binding of the sample is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the sample and is nondiffusible. Particular methods of binding include the use of antibodies (which do not sterically block either the ligand binding site or activation sequence when the protein is bound to the support), direct binding to "sticky" or ionic supports, chemical crosslinking, the synthesis of the protein or agent on the surface, etc. Following binding of the sample, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

The compounds of the invention may be used on their own to inhibit the activity of a mitotic kinesin, particularly KSP. In one embodiment, a compound of the invention is combined with KSP and the activity of KSP is assayed. Kinesin (including KSP) activity is known in the art and includes one or more kinesin activities. Kinesin activities include the ability to affect ATP hydrolysis; microtubule binding; gliding and polymerization/depolymerization (effects on microtubule dynamics); binding to other proteins of the spindle; binding to proteins involved in cell-cycle control; serving as a substrate to other enzymes, such as kinases or proteases; and specific kinesin cellular activities such as spindle pole separation.

Methods of performing motility assays are well known to those of skill in the art. (See e.g., Hall, et al. (1996), *Biophys. J.*, 71: 3467-3476, Turner et al., 1996, *AnaL Biochem.* 242 (1):20-5; Gittes et al., 1996, *Biophys. J.* 70(1): 418-29; Shirakawa et al., 1995, *J. Exp. BioL* 198: 1809-15; Winkelmann et al., 1995, *Biophys. J.* 68: 2444-53; Winkelmann et al., 1995, *Biophys. J.* 68: 72S.)

Methods known in the art for determining ATPase hydrolysis activity also can be used. Suitably, solution based assays are utilized. U.S. Patent 6,410,254, hereby

incorporated by reference in its entirety, describes such assays. Alternatively, conventional methods are used. For example, P_i release from kinesin can be quantified. In one embodiment, the ATPase hydrolysis activity assay utilizes 0.3 M PCA (perchloric acid) and malachite green reagent (8.27 mM sodium molybdate II, 0.33 mM malachite green oxalate, and 0.8 mM Triton X-100). To perform the assay, 10 μ L of the reaction mixture is quenched in 90 μ L of cold 0.3 M PCA. Phosphate standards are used so data can be converted to mM inorganic phosphate released. When all reactions and standards have been quenched in PCA, 100 μ L of malachite green reagent is added to the relevant wells in e.g., a microtiter plate. The mixture is developed for 10-15 minutes and the plate is read at an absorbance of 650 nm. If phosphate standards were used, absorbance readings can be converted to mM P_i and plotted over time. Additionally, ATPase assays known in the art include the luciferase assay.

ATPase activity of kinesin motor domains also can be used to monitor the effects of agents and are well known to those skilled in the art. In one embodiment ATPase assays of kinesin are performed in the absence of microtubules. In another embodiment, the ATPase assays are performed in the presence of microtubules. Different types of agents can be detected in the above assays. In one embodiment, the effect of an agent is independent of the concentration of microtubules and ATP. In another embodiment, the effect of the agents on kinesin ATPase can be decreased by increasing the concentrations of ATP, microtubules or both. In yet another embodiment, the effect of the agent is increased by increasing concentrations of ATP, microtubules or both.

Compounds that inhibit the biochemical activity of KSP in vitro may then be screened in vivo. In vivo screening methods include assays of cell cycle distribution, cell viability, or the presence, morphology, activity, distribution, or number of mitotic spindles. Methods for monitoring cell cycle distribution of a cell population, for example, by flow cytometry, are well known to those skilled in the art, as are methods for determining cell viability. See for example, U.S. Patent 6,437,115, hereby incorporated by reference in its entirety. Microscopic methods for monitoring spindle formation and malformation are well known to those of skill in the art (see, e.g., Whitehead and Rattner (1998), J. Cell Sci. 111:2551-61; Galgio et al, (1996) J. Cell Biol., 135:399-414), each incorporated herein by reference in its entirety.

The compounds of the invention inhibit the KSP kinesin. One measure of inhibition is IC_{50} , defined as the concentration of the compound at which the activity of KSP is decreased by fifty percent relative to a control. Preferred compounds have IC_{50} 's of less than about 1 mM, with preferred embodiments having IC_{50} 's of less than about 100 μ M, with more preferred embodiments having IC_{50} 's of less than about 10 μ M, with particularly preferred embodiments having IC_{50} 's of less than about 1 μ M, and especially preferred embodiments having IC_{50} 's of less than about 100 nM, and with the most preferred embodiments having IC_{50} 's of less than about 10 nM. Measurement of IC_{50} is done using an ATPase assay such as described herein.

Another measure of inhibition is K_i . For compounds with IC_{50} 's less than 1 μ M, the K_i or K_d is defined as the dissociation rate constant for the interaction of the compounds described herein with KSP. Preferred compounds have K_i 's of less than about 100 μ M, with preferred embodiments having K_i 's of less than about 10 μ M, and particularly preferred embodiments having K_i 's of less than about 1 μ M and especially preferred embodiments having K_i 's of less than about 100 nM, and with the most preferred embodiments having K_i 's of less than about 10 nM.

The K_i for a compound is determined from the IC_{50} based on three assumptions and the Michaelis-Menten equation. First, only one compound molecule binds to the enzyme and there is no cooperativity. Second, the concentrations of active enzyme and the compound tested are known (i.e., there are no significant amounts of impurities or inactive forms in the preparations). Third, the enzymatic rate of the enzyme-inhibitor complex is zero. The rate (i.e., compound concentration) data are fitted to the equation:

$$V = V_{\max} E_0 \left[I - \frac{(E_0 + I_0 + K_d) - \sqrt{(E_0 + I_0 + K_d)^2 - 4 E_0 I_0}}{2 E_0} \right]$$

where V is the observed rate, V_{\max} is the rate of the free enzyme, I_0 is the inhibitor concentration, E_0 is the enzyme concentration, and K_d is the dissociation constant of the enzyme-inhibitor complex.

Another measure of inhibition is GI_{50} , defined as the concentration of the compound that results in a decrease in the rate of cell growth by fifty percent.

Preferred compounds have GI_{50} 's of less than about 1 mM; those having a GI_{50} of less

than about 20 μM are more preferred; those having a GI_{50} of less than about 10 μM more so; those having a GI_{50} of less than about 1 μM more so; those having a GI_{50} of less than about 100 nM more so; and those having a GI_{50} of less than about 10 nM even more so. Measurement of GI_{50} is done using a cell proliferation assay such as described herein. Compounds of this class were found to inhibit cell proliferation.

In vitro potency of small molecule inhibitors is determined, for example, by assaying human ovarian cancer cells (SKOV3) for viability following a 72-hour exposure to a 9-point dilution series of compound. Cell viability is determined by measuring the absorbance of formazon, a product formed by the bio-reduction of MTS/PMS, a commercially available reagent. Each point on the dose-response curve is calculated as a percent of untreated control cells at 72 hours minus background absorption (complete cell kill).

Anti-proliferative compounds that have been successfully applied in the clinic to treatment of cancer (cancer chemotherapeutics) have GI_{50} 's that vary greatly. For example, in A549 cells, paclitaxel GI_{50} is 4 nM, doxorubicin is 63 nM, 5-fluorouracil is 1 μM , and hydroxyurea is 500 μM (data provided by National Cancer Institute, Developmental Therapeutic Program, <http://dtp.nci.nih.gov/>). Therefore, compounds that inhibit cellular proliferation, irrespective of the concentration demonstrating inhibition, have potential clinical usefulness.

To employ the compounds of the invention in a method of screening for compounds that bind to KSP kinesin, the KSP is bound to a support, and a compound of the invention is added to the assay. Alternatively, the compound of the invention is bound to the support and KSP is added. Classes of compounds among which novel binding agents may be sought include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for candidate agents that have a low toxicity for human cells. A wide variety of assays may be used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

The determination of the binding of the compound of the invention to KSP may be done in a number of ways. In one embodiment, the compound is labeled, for example, with a fluorescent or radioactive moiety, and binding is determined directly. For example, this may be done by attaching all or a portion of KSP to a solid support,

adding a labeled test compound (for example a compound of the invention in which at least one atom has been replaced by a detectable isotope), washing off excess reagent, and determining whether the amount of the label is that present on the solid support. By "labeled" herein is meant that the compound is either directly or indirectly labeled
5 with a label which provides a detectable signal, e.g., radioisotope, fluorescent tag, enzyme, antibodies, particles such as magnetic particles, chemiluminescent tag, or specific binding molecules, etc. Specific binding molecules include pairs, such as biotin and streptavidin, digoxin and antidigoxin etc. For the specific binding members, the complementary member would normally be labeled with a molecule
10 which provides for detection, in accordance with known procedures, as outlined above. The label can directly or indirectly provide a detectable signal.

In some embodiments, only one of the components is labeled. For example, the kinesin proteins may be labeled at tyrosine positions using ^{125}I , or with fluorophores. Alternatively, more than one component may be labeled with different
15 labels; using ^{125}I for the proteins, for example, and a fluorophor for the antimetabolic agents.

The compounds of the invention may also be used as competitors to screen for additional drug candidates. "Candidate agent" or "drug candidate" or grammatical equivalents as used herein describe any molecule, e.g., protein, oligopeptide, small
20 organic molecule, polysaccharide, polynucleotide, etc., to be tested for bioactivity. They may be capable of directly or indirectly altering the cellular proliferation phenotype or the expression of a cellular proliferation sequence, including both nucleic acid sequences and protein sequences. In other cases, alteration of cellular proliferation protein binding and/or activity is screened. Screens of this sort may be
25 performed either in the presence or absence of microtubules. In the case where protein binding or activity is screened, particular embodiments exclude molecules already known to bind to that particular protein, for example, polymer structures such as microtubules, and energy sources such as ATP. Particular embodiments of assays herein include candidate agents which do not bind the cellular proliferation protein in
30 its endogenous native state termed herein as "exogenous" agents. In another embodiment, exogenous agents further exclude antibodies to KSP.

Candidate agents can encompass numerous chemical classes, though typically they are small organic compounds having a molecular weight of more than 100 and

less than about 2,500 daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding and lipophilic binding, and typically include at least an amine, carbonyl-, hydroxyl-, ether, or carboxyl group; often at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof.

Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. For example, numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means. Known pharmacological agents may be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, and/or amidification to produce structural analogs.

Competitive screening assays may be done by combining KSP and a drug candidate in a first sample. A second sample comprises a compound of the present invention, KSP and a drug candidate. This may be performed in either the presence or absence of microtubules. The binding of the drug candidate is determined for both samples, and a change, or difference in binding between the two samples indicates the presence of a drug candidate capable of binding to KSP and potentially inhibiting its activity. That is, if the binding of the drug candidate is different in the second sample relative to the first sample, the drug candidate is capable of binding to KSP.

In a particular embodiment, the binding of the candidate agent to KSP is determined through the use of competitive binding assays. In this embodiment, the competitor is a binding moiety known to bind to KSP, such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there may be competitive binding as between the candidate agent and the binding moiety, with the binding moiety displacing the candidate agent.

In one embodiment, the candidate agent is labeled. Either the candidate agent, or the competitor, or both, is added first to KSP for a time sufficient to allow binding, if present. Incubations may be performed at any temperature which facilitates optimal activity, typically between 4 and 40°C.

5 Incubation periods are selected for optimum activity, but may also be optimized to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

10 In another embodiment, the competitor is added first, followed by the candidate agent. Displacement of the competitor is an indication the candidate agent is binding to KSP and thus is capable of binding to, and potentially inhibiting, the activity of KSP. In this embodiment, either component can be labeled. Thus, for example, if the competitor is labeled, the presence of label in the wash solution
15 indicates displacement by the agent. Alternatively, if the candidate agent is labeled, the presence of the label on the support indicates displacement.

In an alternative embodiment, the candidate agent is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate the candidate agent is bound to KSP with a higher affinity.
20 Thus, if the candidate agent is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate the candidate agent is capable of binding to KSP.

Inhibition is tested by screening for candidate agents capable of inhibiting the activity of KSP comprising the steps of combining a candidate agent with KSP, as
25 above, and determining an alteration in the biological activity of KSP. Thus, in this embodiment, the candidate agent should both bind to KSP (although this may not be necessary), and alter its biological or biochemical activity as defined herein. The methods include both in vitro screening methods and in vivo screening of cells for alterations in cell cycle distribution, cell viability, or for the presence, morphology,
30 activity, distribution, or amount of mitotic spindles, as are generally outlined above. Alternatively, differential screening may be used to identify drug candidates that bind to the native KSP, but cannot bind to modified KSP.

Positive controls and negative controls may be used in the assays. Suitably all

control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of all samples is for a time sufficient for the binding of the agent to the protein. Following incubation, all samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent
5 determined. For example, where a radiolabel is employed, the samples may be counted in a scintillation counter to determine the amount of bound compound.

A variety of other reagents may be included in the screening assays. These include reagents like salts, neutral proteins, e.g., albumin, detergents, etc which may be used to facilitate optimal protein-protein binding and/or reduce non-specific or
10 background interactions. Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., may be used. The mixture of components may be added in any order that provides for the requisite binding.

Administration

15 Accordingly, the compounds of the invention are administered to cells. By "administered" herein is meant administration of a therapeutically effective dose of a compound of the invention to a cell either in cell culture or in a patient. By "therapeutically effective dose" herein is meant a dose that produces the effects for which it is administered. The exact dose will depend on the purpose of the treatment,
20 and will be ascertainable by one skilled in the art using known techniques. As is known in the art, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art. By "cells" herein is meant any cell in
25 which mitosis or meiosis can be altered.

A "patient" for the purposes of the present invention includes both humans and other animals, particularly mammals, and other organisms. Thus the methods are applicable to both human therapy and veterinary applications. In the preferred embodiment the patient is a mammal, and in the most preferred embodiment the
30 patient is human.

Compounds of the invention having the desired pharmacological activity may be administered, preferably as a pharmaceutically acceptable composition comprising an pharmaceutical excipient, to a patient, as described herein. Depending upon the

manner of introduction, the compounds may be formulated in a variety of ways as discussed below. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt.%.

The agents may be administered alone or in combination with other treatments, i.e., radiation, or other chemotherapeutic agents such as the taxane class of agents that appear to act on microtubule formation or the camptothecin class of topoisomerase I inhibitors. When used, other chemotherapeutic agents may be administered before, concurrently, or after administration of a compound of the present invention. In one aspect of the invention, a compound of the present invention is co-administered with one or more other chemotherapeutic agents. By "co-administer" it is meant that the present compounds are administered to a patient such that the present compounds as well as the co-administered compound may be found in the patient's bloodstream at the same time, regardless when the compounds are actually administered, including simultaneously.

The administration of the compounds and compositions of the present invention can be done in a variety of ways, including, but not limited to, orally, subcutaneously, intravenously, intranasally, transdermally, intraperitoneally, intramuscularly, intrapulmonary, vaginally, rectally, or intraocularly. In some instances, for example, in the treatment of wounds and inflammation, the compound or composition may be directly applied as a solution or spray.

Pharmaceutical dosage forms include a compound of Formula Ia or Ib or a pharmaceutically acceptable salt, solvate, or solvate of a salt thereof, and one or more pharmaceutical excipients. As is known in the art, pharmaceutical excipients are secondary ingredients which function to enable or enhance the delivery of a drug or medicine in a variety of dosage forms (e.g.: oral forms such as tablets, capsules, and liquids; topical forms such as dermal, ophthalmic, and otic forms; suppositories; injectables; respiratory forms and the like). Pharmaceutical excipients include inert or inactive ingredients, synergists or chemicals that substantively contribute to the medicinal effects of the active ingredient. For example, pharmaceutical excipients may function to improve flow characteristics, product uniformity, stability, taste, or appearance, to ease handling and administration of dose, for convenience of use, or to control bioavailability. While pharmaceutical excipients are commonly described as being inert or inactive, it is appreciated in the art that there is a relationship between

the properties of the pharmaceutical excipients and the dosage forms containing them.

Pharmaceutical excipients suitable for use as carriers or diluents are well known in the art, and may be used in a variety of formulations. See, e.g., Remington's Pharmaceutical Sciences, 18th Edition, A. R. Gennaro, Editor, Mack Publishing Company (1990); Remington: The Science and Practice of Pharmacy, 20th Edition, A. R. Gennaro, Editor, Lippincott Williams & Wilkins (2000); Handbook of Pharmaceutical Excipients, 3rd Edition, A. H. Kibbe, Editor, American Pharmaceutical Association, and Pharmaceutical Press (2000); and Handbook of Pharmaceutical Additives, compiled by Michael and Irene Ash, Gower (1995), each of which is incorporated herein by reference for all purposes.

Oral solid dosage forms such as tablets will typically comprise one or more pharmaceutical excipients, which may for example help impart satisfactory processing and compression characteristics, or provide additional desirable physical characteristics to the tablet. Such pharmaceutical excipients may be selected from diluents, binders, glidants, lubricants, disintegrants, colors, flavors, sweetening agents, polymers, waxes or other solubility-retarding materials.

Compositions for intravenous administration will generally comprise intravenous fluids, i.e., sterile solutions of simple chemicals such as sugars, amino acids or electrolytes, which can be easily carried by the circulatory system and assimilated. Such fluids are prepared with water for injection USP.

Fluids used commonly for intravenous (IV) use are disclosed in Remington, the Science and Practice of Pharmacy [full citation previously provided], and include:

alcohol (e.g., in dextrose and water ("D/W") [e.g., 5% dextrose] or dextrose and water [e.g., 5% dextrose] in normal saline solution ("NSS"); e.g. 5% alcohol);
synthetic amino acid such as Aminosyn, FreAmine, Travasol, e.g., 3.5 or 7; 8.5; 3.5, 5.5 or 8.5 % respectively;
ammonium chloride e.g., 2.14%;
dextran 40, in NSS e.g., 10% or in D5/W e.g., 10%;
dextran 70, in NSS e.g., 6% or in D5/W e.g., 6%;
dextrose (glucose, D5/W) e.g., 2.5-50%;
dextrose and sodium chloride e.g., 5-20% dextrose and 0.22-0.9% NaCl;
lactated Ringer's (Hartmann's) e.g., NaCl 0.6%, KCl 0.03%, CaCl₂ 0.02%;

- lactate 0.3%;
- mannitol e.g., 5%, optionally in combination with dextrose e.g., 10% or NaCl e.g., 15 or 20%;
- multiple electrolyte solutions with varying combinations of electrolytes,
- 5 dextrose, fructose, invert sugar Ringer's e.g., NaCl 0.86%, KCl 0.03%, CaCl₂ 0.033%;
- sodium bicarbonate e.g., 5%;
- sodium chloride e.g., 0.45, 0.9, 3, or 5%;
- sodium lactate e.g., 1/6 M; and
- 10 sterile water for injection

The pH of such fluids may vary, and will typically be from 3.5 to 8 such as known in the art.

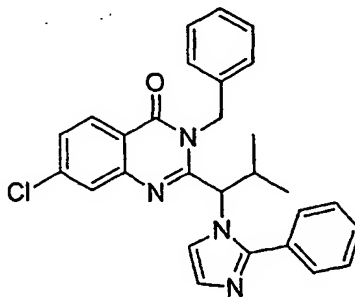
- The following examples serve to more fully describe the manner of using the above-described invention, as well as to set forth the best modes contemplated for
- 15 carrying out various aspects of the invention. It is understood that these examples in no way serve to limit the true scope of this invention, but rather are presented for illustrative purposes. All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated
- 20 by reference herein as though fully set forth.

EXAMPLES

All anhydrous solvents were purchased from Aldrich Chemical Company in SureSeal® containers

Example 1

25



3-Benzyl-7-chloro-2-[2-methyl-1-(2-phenyl-imidazol-1-yl)-propyl]-3H-quinazolin-4-one

a) 3-Benzyl-7-chloro-2-[1-(2,2-dimethoxy-ethylamino)-2-methyl-propyl]-3H-

quinazolin-4-one

To a solution of 2-(1-amino-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (1.87 g, 5.48 mmol) in DMF (30 mL) was added bromoacetaldehyde dimethylacetal (2.78 g, 16.44 mmol) and potassium carbonate (2.27 g, 16.44 mmol)

5 and the resulting suspension was heated at 135°C for 18 h. The cooled reaction was concentrated in vacuo, triturated with methylene chloride to remove any solids, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel; 2:1 hexanes:ethyl acetate) to give the title compound as a pale yellow oil (1.38 g, 59%). MS(ES+) m/e 430 [M+H]⁺.

10 b) N-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]- N-(2,2-dimethoxy-ethyl)-benzamide

A solution of 3-benzyl-7-chloro-2-[1-(2,2-dimethoxy-ethylamino)-2-methyl-propyl]-3H-quinazolin-4-one (505 mg, 1.17 mmol), benzoyl chloride (247 mg, 1.76 mmol), and triethylamine (179 mg, 1.76 mmol) in methylene chloride (10 mL) was

15 stirred at room temperature for 18 h. The reaction was washed sequentially with 0.5 N HCl, water, 5% NaHCO₃, water, and brine. The organic layer was dried (Na₂SO₄) and concentrated to yield the title compound as an orange oil (338 mg, 54%).

MS(ES+) m/e 534 [M+H]⁺.

c) 3-Benzyl-7-chloro-2-[2-methyl-1-(2-phenyl-imidazol-1-yl)-propyl]-3H-quinazolin-4-

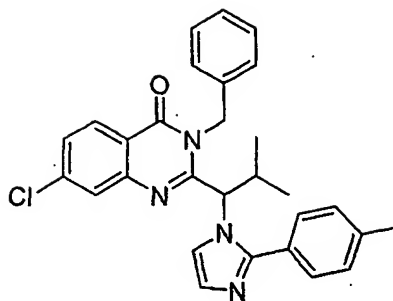
20 one

A solution of N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]- N-(2,2-dimethoxy-ethyl)-benzamide (288 mg, 0.539 mmol) and ammonium acetate (374 mg, 4.85 mmol) in acetic acid (4.0 mL) was refluxed for 2.0 h. The

25 reaction was concentrated in vacuo and the residue was dissolved in ethyl acetate and washed sequentially with saturated sodium carbonate, water, and brine. The organic layer was dried (Na₂SO₄), concentrated in vacuo, and recrystallized from ethanol to give the title compound as tan crystals (57.1 mg, 23%). MS(ES+) m/e 469 [M+H]⁺.

Example 2

3-Benzyl-7-chloro-2-[2-methyl-1-(2-p-tolyl-imidazol-1-yl)-propyl]-3H-quinazolin-4-one

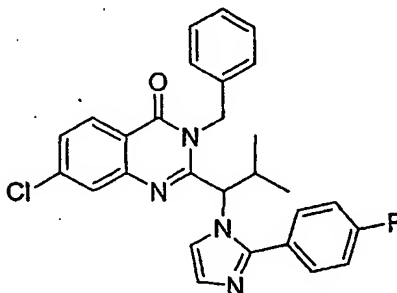


The title compound was prepared as in example one, except substituting p-toluoyl chloride for benzoyl chloride, as a white crystalline solid (22%). MS(ES+) m/e 483

5 [M+H]⁺.

Example 3

3-Benzyl-7-chloro-2-{1-[2-(4-fluorophenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one

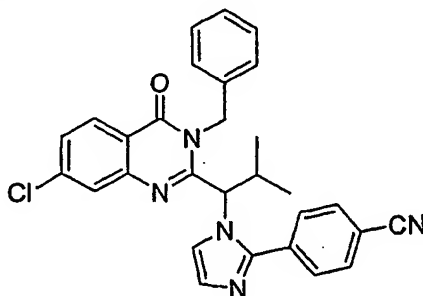


10 The title compound was prepared as in example one, except substituting 4-fluorobenzoyl chloride for benzoyl chloride, as tan crystals (17%). MS(ES+) m/e 487 [M+H]⁺.

Example 4

4-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-1H-imidazol-2-yl}-benzonitrile

15

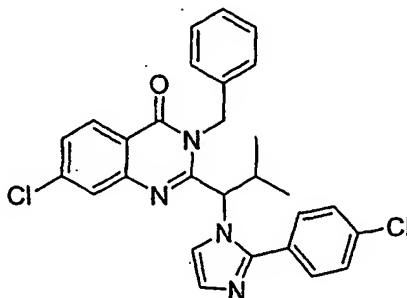


The title compound was prepared as in example one, except substituting 4-cyanobenzoyl chloride for benzoyl chloride and pyridine for methylene chloride, as

tan crystals (18%). MS(ES+) m/e 494 [M+H]⁺.

Example 5

3-Benzyl-7-chloro-2-{1-[2-(4-chloro-phenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one

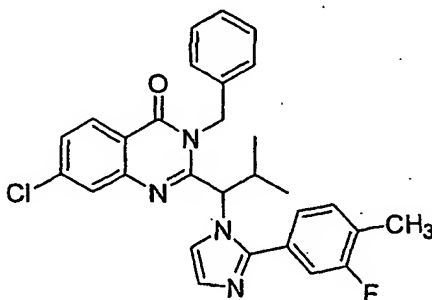


5

The title compound was prepared as in example one, except substituting 4-chlorobenzoyl chloride for benzoyl chloride, as a white solid (24%). MS(ES+) m/e 503 [M+H]⁺.

Example 6

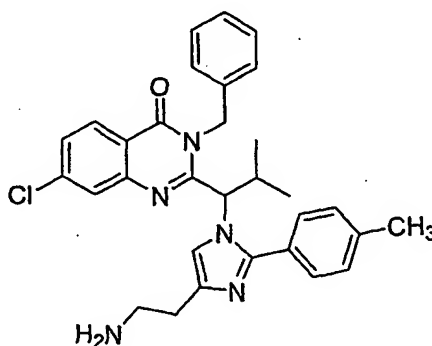
10 **3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one**



The title compound was prepared as in example one, except substituting 3-fluoro-4-methylbenzoyl chloride for benzoyl chloride, as tan crystals (26%). MS(ES+) m/e

15 501 [M+H]⁺.

Example 7



2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-

chloro-3H-quinazolin-4-one

a) 2-{4-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-3-oxo-butyl}-isoindole-1,3-dione

A suspension of 2-(1-amino-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one
5 (1.0 g, 2.93 mmol), 2-(4-bromo-3-oxo-butyl)-isoindole-1,3-dione (867 mg, 2.93 mmol, prepared as described in *WO 89/10360*), and potassium carbonate (405 mg, 2.93 mmol) in DMF (14 mL) was stirred at room temperature for 80 minutes. The reaction was diluted with water and the resulting white solid (1.6 g.) was used in the subsequent step without further purification.

10 b) N-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-N-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-oxo-butyl]-4-methyl-benzamide

A solution of 2-{4-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-3-oxo-butyl}-isoindole-1,3-dione (1.5 g from previous step),
15 triethylamine (245 mg, 2.42 mmol), and p-toluoyl chloride (374 mg, 2.42 mmol) in methylene chloride (10 mL) was stirred at room temperature for 2.0 h. The reaction was washed sequentially with 0.5 N HCl, water, 5% NaHCO₃, water, and brine and dried (Na₂SO₄). The filtrate was concentrated in vacuo and purified by flash chromatography (silica gel 3:2 hexanes:EtOAc as eluent) to provide the title
20 compound as a white solid (0.7 g, 35%, 2 steps). MS(ES+) m/e 675 [M+H]⁺.

c) 2-(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione

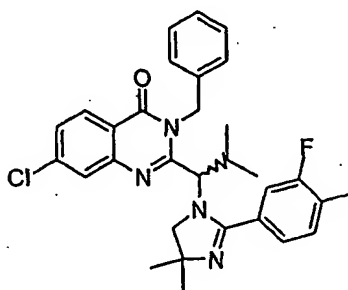
A solution of N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-N-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-oxo-butyl]-4-methyl-
25 benzamide (641 mg, 0.948 mmol) and ammonium acetate (3.65 g, 47.4 mmol) in acetic acid (30 mL) was refluxed for 6.0 h using a Dean-Stark trap and condenser. The reaction was concentrated in vacuo and the residue was triturated with water, dried in a Buchner funnel, and recrystallized from ethanol to provide the title compound as a white solid (320 mg, 51%). MS(ES+) m/e 656 [M+H]⁺.

30 d) 2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one

A solution of 2-(2-{1-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-

methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione (278 mg, 0.423 mmol) and anhydrous hydrazine (98 mg, 3.06 mmol) in EtOH (12 mL) was refluxed for 3.0 h. The reaction was cooled to 5°C and a white precipitate was filtered off. The filtrate was concentrated in vacuo and purified by flash chromatography (silica gel, 90:9:1 methylene chloride:methanol:ammonium hydroxide as eluent) to provide the title compound as a white solid (98.2 mg, 45%). MS(ES+) m/e 526 [M+H]⁺.

Example 8



(±)-3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one.

a) (±)-{2-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-carbamic acid *tert*-butyl ester

To a solution of 2-(1-amino-2-methyl-propyl)-3-benzyl-7-chloro-3 *H*-quinazolin-4-one (WO 0130768) (1.09 g, 3.19 mmol) and (1,1-dimethyl-2-oxo-ethyl)-carbamic acid *tert*-butyl ester (Seki *et. al. Chem. Pharm. Bull.* 1996, 44, 2061) (0.59 g, 3.19 mmol) in dichloromethane (80 mL) was added sodium triacetoxyborohydride (1.01 g, 4.79 mmol). The resultant cloudy mixture was maintained at ambient temperature for 4 hours, at which time it was quenched with brine (75 mL) and stirred vigorously for 10 minutes. The aqueous layer was extracted with dichloromethane (50 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give (±)-{2-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-carbamic acid *tert*-butyl ester (1.62 g, 99%) as a yellow solid which was used in the subsequent step without purification.

b) (±)-2-[1-(2-Amino-2-methyl-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3*H*-quinazolin-4-one

To a solution of (±)-{2-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-carbamic acid *tert*-butyl ester (1.62 g, 3.16 mmol) in dichloromethane (40 mL) was added trifluoroacetic acid (10 mL). The resultant solution was maintained at ambient temperature overnight and concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (40 mL). The aqueous layer was extracted with dichloromethane (50 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure to give (±)-2-[1-(2-amino-2-methyl-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3*H*-quinazolin-4-one (1.29 g, 99%) as a yellow solid which was used in the subsequent step without purification.

Method A:

c) (±)-*N*-{2-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-3-fluoro-4-methyl-benzamide

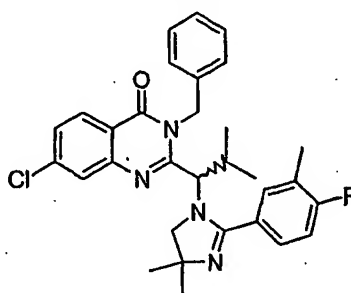
To a solution of (±)-2-[1-(2-amino-2-methyl-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3*H*-quinazolin-4-one (133 mg, 0.32 mmol) in dichloromethane (3 mL) was added triethylamine (90 µL, 0.64 mmol), followed by 3-fluoro-4-methylbenzoyl chloride (51 µL, 0.35 mmol). The resultant solution was stirred at ambient temperature for 3 hours, quenched with saturated aqueous sodium bicarbonate (5 mL) and diluted with dichloromethane (5 mL). The aqueous layer was extracted with dichloromethane (5 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10-20% ethyl acetate/hexanes) to give (±)-*N*-{2-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-3-fluoro-4-methyl-benzamide (120 mg, 68%) as a white solid.

d) (±)-3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3*H*-quinazolin-4-one

A solution of (±)-*N*-{2-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-1,1-dimethyl-ethyl}-3-fluoro-4-methyl-benzamide (120 mg, 0.219 mmol) in phosphorus oxychloride (2 mL) was heated at reflux. After 8 hours, the reaction mixture was allowed to cool to ambient temperature and concentrated

under reduced pressure. The residue was dissolved in dichloromethane (10 mL) and washed with two 10 mL portions of saturated aqueous sodium bicarbonate. The combined aqueous layers were extracted with dichloromethane and the extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (3% methanol/dichloromethane) to give (±)-3-benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one (64 mg, 55%) as a white solid: LCMS 531 ($M^+ + H$)

Example 9



10

Method B:

a) (±)-3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-3-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one

To a solution of (±)-2-[1-(2-amino-2-methyl-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (250 mg, 0.61 mmol) in dichloromethane (10 mL) was added triethylamine (295 μ L, 2.12 mmol), followed by 4-fluoro-3-methylbenzoyl chloride (105 mg, 0.61 mmol). The resultant solution was stirred at ambient temperature for 2 hours, then evaporated under reduced pressure to a crude white solid. The resultant solid was treated with glacial acetic acid (10 mL) then the resultant suspension was heated at reflux for 48 hours. The reaction was cooled to ambient temperature then evaporated under reduced pressure to a crude oil. The oil was quenched with saturated aqueous sodium bicarbonate (10 mL) and brine (5 mL). The aqueous layer was extracted with dichloromethane (2 x 5 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5-10% ethyl acetate/hexanes) to furnish (±)-3-benzyl-7-chloro-2-{1-[2-(4-fluoro-3-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-

imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one (138 mg, 43%) as a white solid: LCMS 531 ($M^+ + H$)

Example 10

By following the procedure described above, the following compounds were prepared:

Compound	Method	MS (ES+) m/e [M+H] ⁺
(±)-3-Benzyl-7-chloro-2-{1-[2-(4-chloro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	533
(±)-3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3H-quinazolin-4-one	A	577
(±)-3-Benzyl-7-chloro-2-{1-[2-(4-methoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	529
(±)-3-Benzyl-7-chloro-2-{1-[4,4-dimethyl-2-(4-trifluoromethyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	567
(±)-3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-thiophen-2-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	505
(±)-3-Benzyl-7-chloro-2-[1-(2-furan-2-yl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	489
(±)-3-Benzyl-7-chloro-2-[1-(2-methoxymethyl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	467
(±)-3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2- <i>m</i> -tolyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	513
(±)-3-Benzyl-7-chloro-2-{1-[2-(3-chloro-phenyl)-4,4-	A	533

dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl]-3H-quinazolin-4-one		
3-Benzyl-7-chloro-2-[(R)-1-(4,4-dimethyl-2- <i>p</i> -tolyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	513
(±)-3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	517
3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-phenyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one trifluoroacetate	A	499
3-Benzyl-7-chloro-2-{1-[2-(3,4-dichloro-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	567
3-Benzyl-7-chloro-2-{1-[2-(3,4-dimethoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	B	559
2-[1-(2-Benzo[1,3]dioxol-5-yl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one	B	543
3-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-benzonitrile	B	524
3-Benzyl-7-chloro-2-{1-[2-(2-chloro-6-methyl-pyridin-4-yl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	B	548
3-Benzyl-7-chloro-2-{1-[4,4-dimethyl-2-(5-methyl-isoxazol-3-yl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	B	504
3-Benzyl-7-chloro-2-{1-[2-(4-fluoro-3-methyl-	B	531

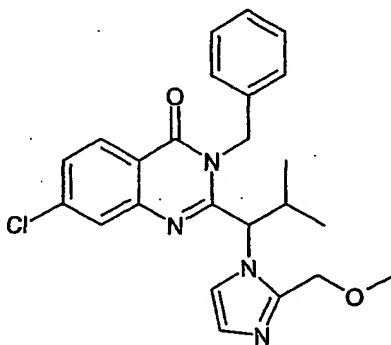
phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one		
3-Benzyl-7-chloro-2-{1-[2-(3,5-dimethoxy-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	B	559
3-Benzyl-7-chloro-2-{1-[2-(2,3-difluoro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	549
3-Benzyl-7-chloro-2-{1-[2-(3-dimethylamino-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	542
3-Benzyl-7-chloro-2-{1-[2-(4-dimethylamino-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	542
3-Benzyl-7-chloro-2-{1-[2-(4-isopropyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	541
3-Benzyl-7-chloro-2-{1-[2-(3-chloro-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	547
3-Benzyl-2-{1-[2-(3-bromo-4-methyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	591
4-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-benzonitrile	A	524
3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-(2-tolyl)-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	513
3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-pyridin-3-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	500

3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-pyridin-4-yl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	500
(±)-3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	503
(±)-3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3H-quinazolin-4-one	A	549
3-Benzyl-7-chloro-2-{1-[(S)-2-(3-fluoro-4-methyl-phenyl)-4-methyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	517
3-Benzyl-7-chloro-2-[2-methyl-1-((S)-4-methyl-2-p-tolyl-4,5-dihydro-imidazol-1-yl)-propyl]-3H-quinazolin-4-one	A	499
3-Benzyl-7-chloro-2-{1-[2-(2-methoxy-ethyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	480
3-Benzyl-7-chloro-2-[1-(2-isopropyl-4,4-dimethyl-4,5-dihydro-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one	A	465
3-Benzyl-7-chloro-2-[1-(4,4-dimethyl-2-quinoxalin-2-yl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl]-3H-quinazolin-4-one	B	550
3-Benzyl-7-chloro-2-{1-[2-(4-ethyl-phenyl)-4,4-dimethyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	B	526
3-Benzyl-7-chloro-2-[(R)-2-methyl-1-(2-p-tolyl-4,5-dihydro-imidazol-1-yl)-propyl]-3H-quinazolin-4-one	A	485
N-(4-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-4,4-dimethyl-4,5-dihydro-1H-imidazol-2-yl}-phenyl)-acetamide	A	556

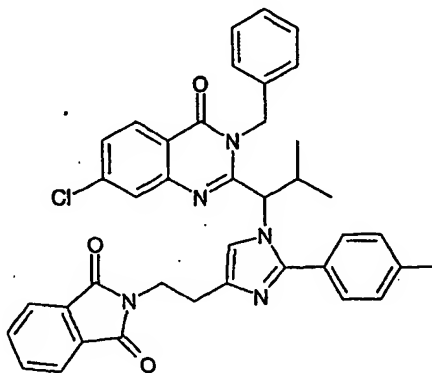
3-Benzyl-7-chloro-2-{1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one	A	503
3-Benzyl-2-{1-[2-(4-bromo-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl}-7-chloro-3H-quinazolin-4-one	A	548
3-Benzyl-7-chloro-2-((R)-1-[2-(3-fluoro-4-methyl-phenyl)-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl)-3H-quinazolin-4-one	A	503

Example 11

3-Benzyl-7-chloro-2-{1-[2-(methoxymethyl)-imidazol-1-yl]-2-methyl-propyl}-3H-quinazolin-4-one



- 5 The title compound was prepared as in example one, except substituting methoxyacetyl chloride for benzoyl chloride, as tan crystals (15%). MS(ES+) m/e 437 [M+H]⁺.

Example 12

- 10 **2-(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione**

a) 2-{4-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-3-oxo-butyl}-isoindole-1,3-dione

A suspension of 2-(1-amino-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (1.0 g, 2.93 mmol), 2-(4-bromo-3-oxo-butyl)-isoindole-1,3-dione (867 mg., 2.93 mmol, prepared as described in *WO 89/10360*), and potassium carbonate (405 mg, 2.93 mmol) in DMF (14 mL) was stirred at room temperature for 80 minutes. The reaction was diluted with water and the resulting white solid (1.6 g) was used in the subsequent step without further purification.

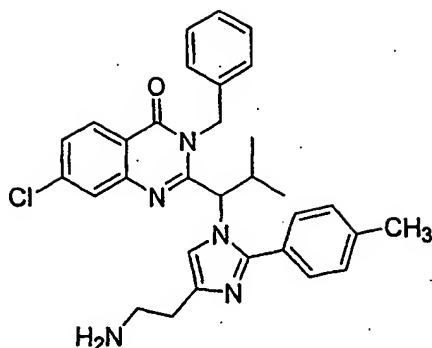
b) N-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-N-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-oxo-butyl]-4-methyl-benzamide

A solution of 2-{4-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-3-oxo-butyl}-isoindole-1,3-dione (1.5 g from previous step), triethylamine (245 mg, 2.42 mmol), and p-toluoyl chloride (374 mg, 2.42 mmol) in methylene chloride (10 mL) was stirred at room temperature for 2.0 h. The reaction was washed sequentially with 0.5 N HCl, water, 5% NaHCO₃, water, and brine and dried (Na₂SO₄). The filtrate was concentrated in vacuo and purified by flash chromatography (silica gel 3:2 hexanes:EtOAc as eluent) to provide the title compound as a white solid (0.7 g, 35%, 2 steps). MS(ES⁺) m/e 675 [M+H]⁺.

c) 2-(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione

A solution of N-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-N-[4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-oxo-butyl]-4-methyl-benzamide (641 mg, 0.948 mmol) and ammonium acetate (3.65 g, 47.4 mmol) in acetic acid (30 mL) was refluxed for 6.0 h using a Dean-Stark trap and condenser. The reaction was concentrated in vacuo and the residue was triturated with water, dried in a Buchner funnel, and recrystallized from ethanol to provide the title compound as a white solid (320 mg, 51%). MS(ES⁺) m/e 656 [M+H]⁺.

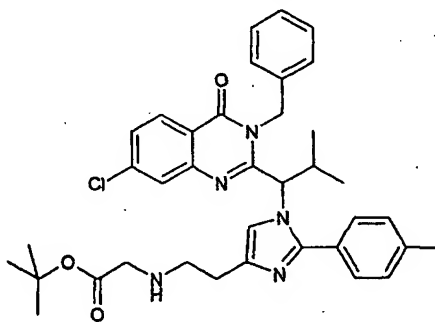
Example 13



2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one

A solution of 2-(2-{1-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethyl)-isoindole-1,3-dione (278 mg, 0.423 mmol) and anhydrous hydrazine (98 mg, 3.06 mmol) in EtOH (12 mL) was refluxed for 3.0 h. The reaction was cooled to 5°C and a white precipitate was filtered off. The filtrate was concentrated in vacuo and purified by flash chromatography (silica gel, 90:9:1 methylene chloride:methanol:ammonium hydroxide as eluent) to provide the title compound as a white solid (98.2 mg, 45%). MS(ES⁺) m/e 526 [M+H]⁺.

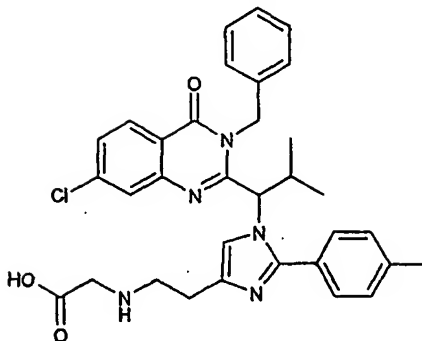
Example 14



(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethylamino)-acetic acid tert-butyl ester

A solution of 2-{1-[4-(2-Amino-ethyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one (181 mg, 0.343 mmol), potassium carbonate (47 mg., 0.343 mmol), and tert-butyl bromoacetate (67 mg., 0.343 mmol) in DMF (2.0 mL) was stirred at room temperature for 4.5 h. The reaction was diluted with water and the resulting white precipitate was filtered and purified by flash chromatography (silica gel, 95:5 methylene chloride: methanol) to provide the title compound as a white solid (109 mg., 50%). MS(ES⁺) m/e 640 [M+H]⁺.

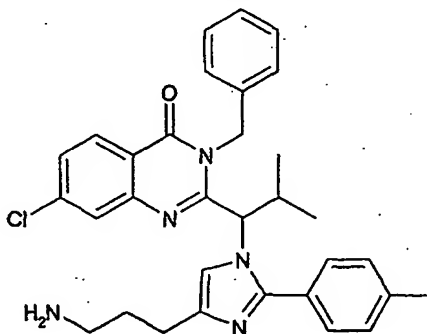
Example 15



(2-{1-[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethylamino)-acetic acid

- 5 A solution of (2-{1-[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-yl}-ethylamino)-acetic acid tert-butyl ester (99.6 mg., 0.155 mmol) and trifluoroacetic acid (8 mL) in methylene chloride (4 mL) was stirred at room temperature for 3.0 h. The reaction was concentrated in vacuo and the residue was triturated with diethyl ether and dried to provide the title
10 compound as a white solid (67 mg., 53%). MS(ES+) m/e 584 $[M+H]^+$.

Example 16

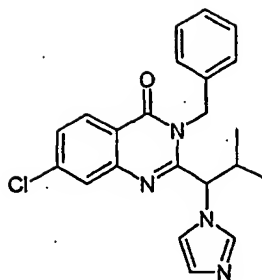


- 2-{1-[4-(3-Amino-propyl)-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one**

15 The title compound was prepared as in example 12 and 13, except substituting 2-(5-bromo-4-oxo-pentyl)-isoindole-1,3-dione for 2-(4-bromo-3-oxo-butyl)-isoindole-1,3-dione (as described in J. Med. Chem. 35, 3239 (1992)), as a white solid (61%). MS(ES+) m/e 540 $[M+H]^+$.

20

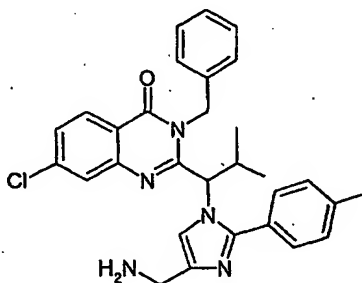
Example 17



(±)-3-Benzyl-7-chloro-2-(1-imidazol-1-yl-2-methyl-propyl)-3H-quinazolin-4-one

To a solution of (±)-3-benzyl-2-(1-bromo-2-methyl-propyl)-7-chloro-3H-quinazolin-4-one (a compound of Formula 105, 250 mg, 0.616 mmol) in DMF (3 mL) was added triethylamine (0.130 mL, 0.924 mmol) and imidazole (63.0 mg, 0.924 mmol) followed by tetrabutylammonium iodide (228 mg, 0.616 mmol). The resultant solution was heated to 90 °C, stirred for 18 h and allowed to cool to room temperature. The reaction mixture was quenched with water (3 mL) and diluted with ether (10 mL). The aqueous layer was extracted with ether (10 mL) and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to provide 38 mg (16%) of the title compound as a yellow solid. MS(ES⁺) m/e 393.0 [M + H]⁺.

Example 18



2-[(R)-1-(4-Aminomethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one

a) 2-[(R)-1-(3-Phthalimido-2-oxo-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one

To 2-[(R)-1-amino-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (5.0 g, 14.6 mMol) and K₂CO₃ (2.1 g, 15.2 mMol) in DMF (50 mL) was added N-(3-Bromo-2-oxopropyl)-phthalimide (4.5 g, 14.8 mMol) (Nair et al.; J. Org. Chem.; 40; 1975; 1745). The reaction was stirred at RT for 3 h, concentrated under vacuum,

taken up in EtOAc, washed with water, brine, dried (Na_2SO_4) and evaporated to give the title compound (7.94 g, 14.6 mMol) as an off-white solid: MS (ES) m/e 543.2 ($\text{M} + \text{H}^+$).

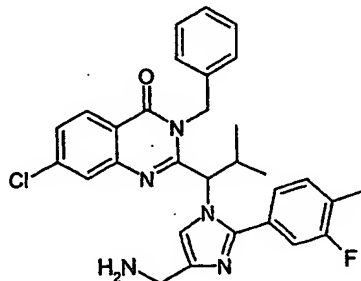
b) 2-[(R)-1-[N-Toluoyl-(3-Phthalimido-2-oxo-propyl)amino]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one
 5 To 2-[(R)-1-(3-phthalimido-2-oxo-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (7.22 g, 13.3 mMol) in CH_2Cl_2 (50 mL) was added Et_3N (2.0 mL, 14.3 mMol) and toluoyl chloride (1.9 mL, 14.4 mMol). The reaction was stirred at RT for 18 h, concentrated under vacuum, taken up in EtOAc, washed with 1 N HCl,
 10 brine, dried (MgSO_4) and evaporated to dryness. Purification by flash chromatography on silica gel (1% MeOH/ CH_2Cl_2) followed by trituration with (1:1) Et_2O /pet. ether, filtration and drying under vacuum gave the title compound (6.41 g, 73%) as a white solid. A side fraction (1.20 g) which contained mostly product was also obtained: ^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, J = 8.6 Hz, 1 H), 7.69 – 7.78 (m, 5 H), 7.45 – 7.49 (m, 3 H), 7.34 (t, 2 H), 7.25 – 7.29 (m, 3 H), 7.15 (d, J = 8.1 Hz, 2 H), 6.19 (d, J = 15.9 Hz, 1 H), 5.82 (d, J = 10.6 Hz, 1 H), 5.12 (d, J = 15.9 Hz, 1 H), 4.56 (d, J = 18.8 Hz, 1 H), 4.26 (d, J = 18.8 Hz, 1 H), 4.09 (d, J = 17.6 Hz, 1 H), 3.90 (d, J = 17.6 Hz, 1 H), 2.62 (m, 1 H), 2.42 (s, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.32 (d, J = 6.4 Hz, 3 H); MS (ES) m/e 661.2 ($\text{M} + \text{H}^+$).

c) N-{1-[(R)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-acetamide (SB-767470) and N-{1-[(R)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-phthalimide
 20 To 2-[(R)-1-[N-toluoyl-(3-phthalimido-2-oxo-propyl)amino]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (6.0 g, 9.1 mMol) and NH_4OAc (35 g, 450 mMol) was added HOAc (100 mL). The reaction was stirred and heated to reflux (155 °C oil bath) for 6 h. After cooling to RT the reaction was concentrated under vacuum and poured into ice water (500 mL). The fine white precipitate which formed was filtered off (slow!), rinsed with water then dried under vacuum. Purification by
 25 flash chromatography on silica gel (50% EtOAc/hexane to EtOAc to 5% MeOH/EtOAc) after trituration with (1:1) Et_2O /pet. ether, filtration and drying under

vacuum gave the title compound N-{1-[(R)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-phthalimide (3.77 g, 65%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.23 (d, $J = 8.6$ Hz, 1 H), 7.87 (m, 2 H), 7.72 (m, 2 H), 7.68 (d, $J = 1.7$ Hz, 1 H), 7.61 (s, 1 H), 7.46 – 7.50 (m, 3 H), 7.40 (d, $J = 7.9$ Hz, 2 H), 7.15 – 7.22 (m, 3 H), 6.47 (d, $J = 7.0$ Hz, 2 H), 5.75 (d, $J = 16.3$ Hz, 1 H), 4.89 (m, 3 H), 3.79 (d, $J = 16.3$ Hz, 1 H), 2.93 (m, 1 H), 2.52 (s, 3 H), 0.89 (d, $J = 6.8$ Hz, 3 H), 0.25 (d, $J = 6.8$ Hz, 3 H); MS (ES) m/e 642.2 ($M + H$) $^+$.

d) 2-[(R)-1-(4-Aminomethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one
 To N-{1-[(R)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-phthalimide (3.50 g, 5.5 mMol) in EtOH (100 mL) was added hydrazine monohydrate (1.1 mL, 22.7 mMol). The reaction was stirred at RT for 72 h, filtered through a pad of Celite[®] to remove the insoluble precipitate, rinsed with EtOH and evaporated to dryness. Purification by flash chromatography on silica gel [5 – 10% (5% NH_4OH in $\text{MeOH}/\text{CH}_2\text{Cl}_2$)] gave the title compound (2.71 g, 96%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.6$ Hz, 1 H), 7.80 (d, $J = 2.0$ Hz, 1 H), 7.40 – 7.51 (m, 6 H), 7.15 – 7.22 (m, 3 H), 6.43 (d, $J = 7.1$ Hz, 2 H), 5.78 (d, $J = 16.3$ Hz, 1 H), 4.84 (d, $J = 10.5$ Hz, 1 H), 3.87 (d, $J = 16.3$ Hz, 1 H), 3.83 (2d, 2H), 3.00 (m, 1 H), 2.60 (br s, 2 H), 2.54 (s, 3 H), 0.90 (d, $J = 6.7$ Hz, 3 H), 0.31 (d, $J = 6.7$ Hz, 3 H); MS (ES) m/e 512.2 ($M + H$) $^+$.

Example 19

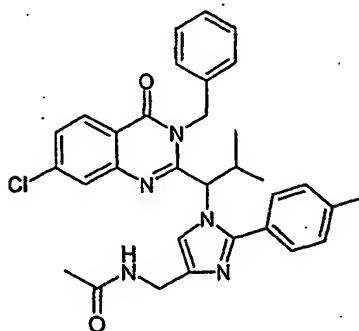


2-[(R)-1-[4-Aminomethyl-2-(3-fluoro-4-methyl-benzoyl)-imidazol-1-yl]-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one

According to the procedure of Example 18, the title compound (191 mg, 61%)

was prepared as an off-white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.6$ Hz, 1 H), 7.81 (d, $J = 1.9$ Hz, 1 H), 7.49 (m, 2 H), 7.41 (app t, 1 H), 7.19 – 7.32 (m, 5 H), 6.48 (d, $J = 6.7$ Hz, 2 H), 5.81 (d, $J = 16.4$ Hz, 1 H), 4.88 (d, $J = 10.5$ Hz, 1 H), 3.90 (d, $J = 16.4$ Hz, 1 H), 3.85 (2d, 2H), 3.02 (m, 1 H), 2.82 (br s, 2 H), 2.46 (s, 3 H), 0.90 (d, $J = 6.7$ Hz, 3 H), 0.37 (d, $J = 6.7$ Hz, 3 H); MS (ES) m/e 530.2 ($M + H$) $^+$.

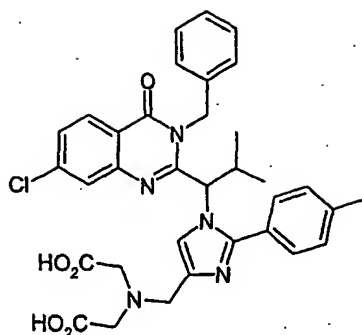
Example 20



N-{1-[(R)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-acetamide

A second product was isolated during the chromatographic purification of Example 18c, which was triturated with Et_2O , filtered and dried under vacuum to give the title compound N-{1-[(R)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-p-tolyl-1H-imidazol-4-ylmethyl}-acetamide (0.87 g, 17%) as a white solid: ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J = 8.6$ Hz, 1 H), 7.80 (d, $J = 2.0$ Hz, 1 H), 7.49 – 7.51 (m, 4 H), 7.43 (d, $J = 8.0$ Hz, 2 H), 7.16 – 7.23 (m, 3 H), 6.43 (d, $J = 7.1$ Hz, 2 H), 6.30 (br s, 1 H), 5.80 (d, $J = 16.3$ Hz, 1 H), 4.87 (d, $J = 10.6$ Hz, 1 H), 4.40 (d, 1 H), 4.36 (d, 1 H), 3.84 (d, $J = 16.3$ Hz, 1 H), 3.00 (m, 1 H), 2.56 (s, 3 H), 1.98 (s, 3 H), 0.90 (d, $J = 6.8$ Hz, 3 H), 0.30 (d, $J = 6.6$ Hz, 3 H); MS (ES) m/e 554.2 ($M + H$) $^+$.

Example 21



2-((R)-1-[4-(N,N-Dicarboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one

- a) 2-((R)-1-[4-(N,N-Di-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one and 2-((R)-1-[4-(N-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one

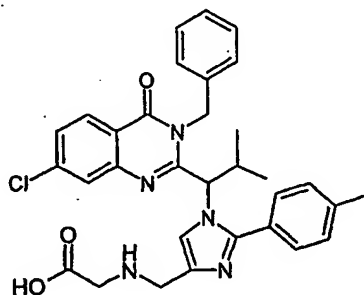
To 2-((R)-1-(4-aminomethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (0.35 g, 0.68 mMol) (from example 18d) and K_2CO_3 (100 mg, 0.72 mMol) in DMF (10 mL) was added t-butyl bromoacetate (103 μ L, 0.68 mMol). The reaction was stirred at RT for 18 h, concentrated under vacuum, triturated with cold water, filtered and dried under vacuum. Purification by flash chromatography on silica gel (1-5% (5% NH_4OH in MeOH)/(20% EtOAc in CH_2Cl_2) gave the title compound 2-((R)-1-[4-(N,N-di-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (0.23 g, 46%) as a white solid: MS (ES) m/e 740.2 (M + H)⁺.

b) 2-((R)-1-[4-(N,N-Dicarboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one

To 2-((R)-1-[4-(N,N-di-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (0.23 g, 0.31 mMol) was added TFA (20 mL). The reaction was stirred at RT for 4 h and evaporated to dryness under vacuum. Trituration with (1:1) Et₂O/pet. ether, filtration and drying under vacuum gave the title compound 2-((R)-1-[4-(N,N-dicarboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (203 mg, 77%) as a white solid: ¹H NMR (400 MHz, d₆-

DMSO) δ 8.19 (d, J = 8.6 Hz, 1 H), 8.14 (s, 1 H), 7.91 (d, J = 1.8 Hz, 1 H), 7.68 (dd, 1 H), 7.52 – 7.55 (m, 4 H), 7.21 – 7.25 (m, 3 H), 6.50 (d, J = 5.9 Hz, 2 H), 5.59 (d, J = 16.7 Hz, 1 H), 4.88 (d, J = 10.1 Hz, 1 H), 4.13 (d, J = 14.6 Hz, 1 H), 4.05 (d, J = 14.6 Hz, 1 H), 4.00 (d, J = 16.8 Hz, 1 H), 3.68 (s, 4 H), 2.78 (m, 1 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.26 (d, J = 6.5 Hz, 3 H).

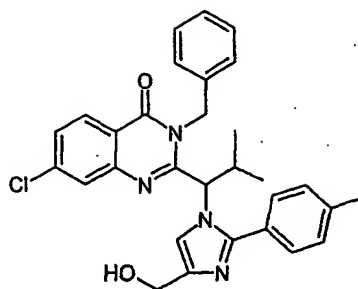
Example 22



2-((R)-1-[4-(N-Carboxymethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one

During the chromatographic purification of Example 21a, second compound, 2-((R)-1-[4-(N-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one, was obtained (0.10 g, 24%) as a white solid: MS (ES) m/e 626.2 ($M + H$)⁺. According to the procedure of Example 20b, 2-((R)-1-[4-(N-t-butoxycarbonylmethyl)aminomethyl-2-p-tolyl-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3H-quinazolin-4-one (0.10 g, 0.16 mMol) was converted to the title compound (102 mg, 80%) as a white solid: ¹H NMR (400 MHz, d_6 -DMSO) δ 8.18 (d, J = 8.5 Hz, 1 H), 7.88 (d, J = 1.8 Hz, 1 H), 7.86 (s, 1 H), 7.67 (dd, 1 H), 7.41 – 7.57 (m, 4 H), 7.22 – 7.27 (m, 3 H), 6.46 (d, J = 7.5 Hz, 2 H), 5.56 (d, J = 16.7 Hz, 1 H), 4.84 (d, J = 10.3 Hz, 1 H), 4.15 (d, J = 13.7 Hz, 1 H), 4.10 (d, J = 13.8 Hz, 1 H), 4.02 (d, J = 16.6 Hz, 1 H), 3.89 (s, 2 H), 2.85 (m, 1 H), 0.80 (d, J = 6.7 Hz, 3 H), 0.34 (d, J = 6.7 Hz, 3 H).

Example 23



3-Benzyl-7-chloro-2-[(R)-1-(4-hydroxymethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one

a) 2-[(R)-1-(3-Toluoyloxy-2-oxo-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one

To 2-[(R)-1-amino-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (1.0 g, 2.9 mMol) in DMF (10 mL) was added DIEA (0.6 mL, 3.4 mMol) and 1-toluoyloxy-3-bromopropan-2-one (1.0 g, 3.7 mMol) (Prepared using the procedure of F. C. Hartman, *Biochemistry*, 9, 1776 (1970) except substituting toluoyl chloride for benzoyl chloride.) The reaction was stirred at RT for 18 h, concentrated under vacuum, taken up in EtOAc, washed with 1 N Na₂CO₃, dried (Na₂SO₄) and evaporated to dryness. The product was converted to its hydrochloride salt by treating with 4 N HCl in dioxane (20 mL) and concentration under vacuum. Trituration with (1:1) Et₂O/pet. ether, filtration and drying under vacuum left the title compound (1.87 g, 100%, 88% pure) as a beige solid: MS (ES) m/e 532.2 (M + H)⁺.

b) 2-{(R)-1-[N-Toluoyl-(3-toluoyloxy-2-oxo-propyl)amino]-2-methyl-propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one

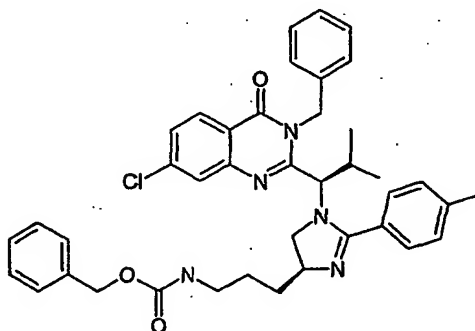
To 2-[(R)-1-(3-toluoyloxy-2-oxo-propylamino)-2-methyl-propyl]-3-benzyl-7-chloro-3H-quinazolin-4-one (1.87 g, 2.9 mMol) in CH₂Cl₂ (30 mL) was added Et₃N (1 mL, 7.1 mMol) and toluoyl chloride (0.44 mL, 3.3 mMol). The reaction was stirred at RT for 18 h, concentrated under vacuum, taken up in EtOAc, washed with 1 N HCl, brine, dried (MgSO₄) and evaporated to dryness. Purification by flash chromatography on silica gel (20% EtOAc/hexane) gave the title compound (1.76 g, 93%) as a white solid: MS (ES) m/e 650.4 (M + H)⁺.

c) 3-Benzyl-7-chloro-2-[(R)-1-(4-hydroxymethyl-2-p-tolyl-imidazol-1-yl)-2-methyl-propyl]-3H-quinazolin-4-one (SB-792813)

To a mixture of 2-{(R)-1-[N-toluoyl-(3-toluoyloxy-2-oxo-propyl)amino]-2-methyl-

propyl}-3-benzyl-7-chloro-3H-quinazolin-4-one (1.50 g, 2.3 mMol) and NH₄OAc (8.9 g, 115 mMol) was added HOAc (30 mL). The reaction was heated to reflux (155 °C oil bath) and stirred for 2.5 h. After cooling to RT the reaction was concentrated under vacuum, taken up in EtOAc, washed with water, 1 N Na₂CO₃, brine, dried (MgSO₄) and evaporated to dryness. To this crude mixture of alcohol, toluoyl and acetyl esters was added MeOH (20 mL) and 1 N NaOH (5 mL). The reaction was stirred at RT for 18 h, neutralized with 1 N HCl (5 mL) and evaporated under vacuum. The remaining solid was taken up in EtOAc, washed with water, brine, dried (MgSO₄) and evaporated to dryness. Purification by flash chromatography on silica gel (80-100% EtOAc/hexane) gave the title compound (0.95 g, 81%) as an off-white solid: ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 8.6 Hz, 1 H), 7.78 (d, J = 1.8 Hz, 1 H), 7.48 – 7.54 (m, 4 H), 7.43 (d, J = 7.9 Hz, 2 H), 7.16 – 7.23 (m, 3 H), 6.43 (d, J = 7.2 Hz, 2 H), 5.78 (d, J = 16.3 Hz, 1 H), 4.88 (d, J = 10.5 Hz, 1 H), 4.64 (d, J = 12.9 Hz, 1 H), 4.60 (d, J = 12.9 Hz, 1 H), 3.84 (d, J = 16.3 Hz, 1 H), 3.01 (m, 1 H), 2.75 (br s, 1 H), 2.55 (s, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.32 (d, J = 6.7 Hz, 3 H); MS (ES) m/e 513.2 (M + H)⁺.

Example 24



(3-((*S*)-1-[(*R*)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-*p*-tolyl-4,5-dihydro-1*H*-imidazol-4-yl)-propyl)-carbamic acid benzyl ester

a) ((*S*)-1-{[(*R*)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-methyl}-4-benzoyloxycarbonylamino-butyl)-carbamic acid *tert*-butyl ester

To a solution of 2-((*R*)-1-amino-2-methyl-propyl)-3-benzyl-7-chloro-3*H*-quinazolin-4-one (a compound of Formula 107, 366 mg, 1.07 mmol) and ((*S*)-4-

benzyloxycarbonylamino-1-formyl-butyl)-carbamic acid *tert*-butyl ester (prepared as previously described: Hamada, Y.; Shioro, T. *Chem. Pharm. Bull.* 1982, 30, 1921) (452 mg, 1.29 mmol) in CH₂Cl₂ (25 mL) was added sodium triacetoxymethylborohydride (341 mg, 1.61 mmol). The resultant cloudy mixture was stirred overnight and
5 quenched with saturated brine (50 mL). The aqueous layer was extracted with CH₂Cl₂ (20 mL) and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2:1 hexanes:ethyl acetate) to provide 550 mg (76%) of the title compound as a yellow oil. MS(ES+) *m/e* 676.4 [M + H]⁺.

10 b) (1-{[1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-(1-*p*-tolyl-methanoyl)-amino]-methyl}-4-benzyloxycarbonylamino-butyl)-carbamic acid *tert*-butyl ester

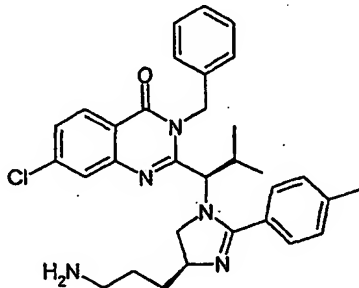
To a solution of ((*S*)-1-{[(*R*)-1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propylamino]-methyl}-4-benzyloxycarbonylamino-butyl)-carbamic acid
15 *tert*-butyl ester (250 mg, 0.37 mmol) in toluene (4 mL) was added triethylamine (0.10 mL, 0.74 mmol) followed by dropwise addition of *p*-toluoyl chloride (0.049 mL, 0.37 mmol). The reaction mixture was heated to 80 °C for 18 h, then reflux for 4 h. The reaction mixture was allowed to cool to room temperature, quenched with saturated aqueous NaHCO₃ (10 mL) and diluted with CH₂Cl₂ (10 mL). The extracts were dried
20 over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (3:1 hexanes:ethyl acetate) to provide 235 mg (79%) of the title compound as a pale yellow powder. MS(ES+) *m/e* 794.2 [M + H]⁺.

25 c) (3-{(*S*)-1-[(*R*)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-*p*-tolyl-4,5-dihydro-1*H*-imidazol-4-yl}-propyl)-carbamic acid benzyl ester

A solution of (1-{[1-(3-benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-(1-*p*-tolyl-methanoyl)-amino]-methyl}-4-benzyloxycarbonylamino-butyl)-carbamic acid *tert*-butyl ester (235 mg, 0.37 mmol) in CH₂Cl₂/TFA (4:1, 5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated
30 under reduced pressure and the residue was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was diluted with THF (10 mL) and saturated

aqueous NaHCO₃ (1 mL). The mixture was stirred at room temperature for 10 days, diluted with ether (20 mL) and washed with brine. The aqueous layer was extracted with two 10 mL portions of EtOAc and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (19:1 CH₂Cl₂:MeOH) to provide 81 mg (40%) of the title compound as a pale white powder. MS(ES⁺) m/e 675.6 [M + H]⁺.

Example 25



2-((*R*)-1-[(*S*)-4-(3-Amino-propyl)-2-*p*-tolyl-4,5-dihydro-imidazol-1-yl]-2-methyl-propyl)-3-benzyl-7-chloro-3*H*-quinazolin-4-one

(3-((*S*)-1-[(*R*)-1-(3-Benzyl-7-chloro-4-oxo-3,4-dihydro-quinazolin-2-yl)-2-methyl-propyl]-2-*p*-tolyl-4,5-dihydro-1*H*-imidazol-4-yl)-propyl)-carbamic acid benzyl ester (65.0 mg, 0.096 mmol) was dissolved in a solution of HBr in AcOH (30% by weight, 5 mL). After 45 min, the reaction mixture was concentrated under reduced pressure. The residue was diluted with toluene (2 mL) and concentrated under reduced pressure. The residue was then diluted with CH₂Cl₂ (10 mL) and washed with 1N NaOH (10 mL). The aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL) and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (92:7:1 CH₂Cl₂:MeOH:NH₄OH) to provide 30.0 mg (57%) of the title compound as an off-white powder. MS(ES⁺) m/e 542.2 [M + H]⁺.

Example 26

Inhibition of Cellular Viability in Tumor Cell Lines Treated with KSP

Inhibitors.r

25 Materials and Solutions:

Cells: SKOV3, Ovarian Cancer (human).

Media: Phenol Red Free RPMI + 5% Fetal Bovine Serum + 2mM L-glutamine.

Colorimetric Agent for Determining Cell Viability: Promega MTS tetrazolium

compound.

Control Compound for max cell kill: Topotecan, 1 μ M.

Procedure: Day 1 - Cell Plating:

Adherent SKOV3 cells are washed with 10mLs of PBS followed by the addition of
5 2mLs of 0.25% trypsin and incubation for 5 minutes at 37°C. The cells are rinsed
from the flask using 8 mL of media (phenol red-free RPMI+ 5%FBS) and transferred
to fresh flask. Cell concentration is determined using a Coulter counter and the
appropriate volume of cells to achieve 1000 cells/100 μ L is calculated. 100 μ L of
media cell suspension (adjusted to 1000 cells/100 μ L) is added to all wells of 96-well
10 plates, followed by incubation for 18 to 24 hours at 37°C, 100% humidity, and 5%
CO₂, allowing the cells to adhere to the plates.

Procedure: Day 2 – Compound Addition:

To one column of the wells of an autoclaved assay block are added an initial
2.5 μ L of test compound(s) at 400X the highest desired concentration. 1.25 μ L of
15 400X (400 μ M) Topotecan is added to other wells (optical density's from these wells
are used to subtract out for background absorbance of dead cells and vehicle). 500 μ L
of media without DMSO are added to the wells containing test compound, and 250 μ L
to the Topotecan wells. 250 μ L of media + 0.5% DMSO is added to all remaining
wells, into which the test compound(s) are serially diluted. By row, compound-
20 containing media is replica plated (in duplicate) from the assay block to the
corresponding cell plates. The cell plates are incubated for 72 hours at 37°C, 100%
humidity, and 5% CO₂.

Procedure: Day 4 – MTS Addition and OD Reading:

The plates are removed from the incubator and 40 μ L MTS / PMS is added to
25 each well. Plates are then incubated for 120 minutes at 37°C, 100% humidity,
5%CO₂, followed by reading the ODs at 490nm after a 5 second shaking cycle in a
ninety-six well spectrophotometer.

Data Analysis

The normalized % of control (absorbance- background) is calculated and an
30 XLfit is used to generate a dose-response curve from which the concentration of
compound required to inhibit viability by 50% is determined. The compounds of the
present invention show activity when tested by this method as described above.

Example 27

Enantiomer Separation

In general, the procedures described above can be used to prepare substantially pure or enriched R- or S-enantiomers by selecting a starting amino acid of the appropriate R- or S-configuration. More preferred compounds of the invention are those of the R-configuration at the stereogenic center to which R² is attached. An R:S mixture can be separated into its constituent pure enantiomers by methods well known to those skilled in the art. These include the formation and separation of diastereomeric derivatives such as those formed by reaction with an optically pure acid such as dibenzoyltartaric acid. Alternatively, separation can be accomplished by chiral chromatography, for example, using the following conditions:

Column: Chiralcel OD 20 x 250 mm;

Sample loaded ~100 mg mL⁻¹ in 1:2 ethanol:hexane containing 0.01% isopropylamine;

Chromatography conditions: isocratic elution with 1:2 ethanol:hexane containing 0.01% isopropylamine at a flow rate of 15 mL min⁻¹; UV detection at 254 nm.

For example, an enriched 3:1 R:S mixture of enantiomers was separated into its pure enantiomers by chiral chromatography with the following conditions: Chiralpak AD, 250 x 4.6 mm (Diacel Inc.). Sample – 22.5 mg/ml in 1:1 *i*-PrOH:hexanes. Conditions – 40 min at isocratic 50% *i*-PrOH in Hexanes, (S)-enantiomer elutes at 18.35 min, (R)-enantiomer elutes at 26.87 min. The (R)-enantiomer was significantly more potent than the (S)-enantiomer.

Example 28

25 Monopolar Spindle Formation following Application of a KSP Inhibitor

Human tumor cells Skov-3 (ovarian) were plated in 96-well plates at densities of 4,000 cells per well, allowed to adhere for 24 hours, and treated with various concentrations of the pyridimidinone derivatives for 24 hours. Cells were fixed in 4% formaldehyde and stained with antitubulin antibodies (subsequently recognized using fluorescently-labeled secondary antibody) and Hoechst dye (which stains DNA). Visual inspection revealed that the compounds caused cell cycle arrest in the prometaphase stage of mitosis. DNA was condensed and spindle formation had initiated, but arrested cells uniformly displayed monopolar spindles, indicating that

there was an inhibition of spindle pole body separation. Microinjection of anti-KSP antibodies also causes mitotic arrest with arrested cells displaying monopolar spindles.

Example 29

Inhibition of Cellular Proliferation in Tumor Cell Lines Treated with KSP

5 Inhibitors.

Cells were plated in 96-well plates at densities from 1000-2500 cells/well of a 96-well plate and allowed to adhere/grow for 24 hours. They were then treated with various concentrations of drug for 48 hours. The time at which compounds are added is considered T_0 . A tetrazolium-based assay using the reagent 3-(4,5-dimethylthiazol-10 2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulphophenyl)-2H-tetrazolium (MTS) (Patent No. 5,185,450) (see Promega product catalog #G3580, CellTiter 96® AQueous One Solution Cell Proliferation Assay) was used to determine the number of viable cells at T_0 and the number of cells remaining after 48 hours compound exposure. The number of cells remaining after 48 hours was compared to the number of viable cells at the 15 time of drug addition, allowing for calculation of growth inhibition.

The growth over 48 hours of cells in control wells that had been treated with vehicle only (0.25% DMSO) is considered 100% growth and the growth of cells in wells with compounds is compared to this.

A Gi_{50} was calculated by plotting the concentration of compound in μM vs the 20 percentage of cell growth in treated wells. The Gi_{50} calculated for the compounds is the estimated concentration at which growth is inhibited by 50% compared to control, i.e., the concentration at which:

$$100 \times [(Treated_{48} - T_0) / (Control_{48} - T_0)] = 50$$

wherein $Treated_{48}$ is the value at 48 hours for the treated cells and $Control_{48}$ is the 25 value at 48 hours for the control population.

All concentrations of compounds are tested in duplicate and controls are averaged over 12 wells. A very similar 96-well plate layout and Gi_{50} calculation scheme is used by the National Cancer Institute (see Monks, et al., J. Natl. Cancer Inst. 83:757-766 (1991)). However, the method by which the National Cancer 30 Institute quantitates cell number does not use MTS, but instead employs alternative methods.

Compounds of examples above inhibited cell proliferation in human ovarian tumor cell lines (SKOV-3).

Example 30

Calculation of IC₅₀:

Measurement of a compound's IC₅₀ for KSP activity uses an ATPase assay.

The following solutions are used: Solution 1 consists of 3 mM phosphoenolpyruvate potassium salt (Sigma P-7127), 2 mM ATP (Sigma A-3377), 1 mM IDTT (Sigma D-9779), 5 µM paclitaxel (Sigma T-7402), 10 ppm antifoam 289 (Sigma A-8436), 25 mM Pipes/KOH pH 6.8 (Sigma P6757), 2 mM MgCl₂ (VWR JT400301), and 1 mM EGTA (Sigma E3889). Solution 2 consists of 1 mM NADH (Sigma N8129), 0.2 mg/ml BSA (Sigma A7906), pyruvate kinase 7U/ml, L-lactate dehydrogenase 10 U/ml (Sigma P0294), 100 nM KSP motor domain, 50 µg/ml microtubules, 1 mM DTT (Sigma D9779), 5 µM paclitaxel (Sigma T-7402), 10 ppm antifoam 289 (Sigma A-8436), 25 mM Pipes/KOH pH 6.8 (Sigma P6757), 2 mM MgCl₂ (VWR JT4003-01), and 1 mM EGTA (Sigma E3889). Serial dilutions (8-12 two-fold dilutions) of the compound are made in a 96-well microtiter plate (Corning Costar 3695) using Solution 1. Following serial dilution each well has 50 µl of Solution 1. The reaction is started by adding 50 µl of solution 2 to each well. This may be done with a multichannel pipettor either manually or with automated liquid handling devices. The microtiter plate is then transferred to a microplate absorbance reader and multiple absorbance readings at 340 nm are taken for each well in a kinetic mode. The observed rate of change, which is proportional to the ATPase rate, is then plotted as a function of the compound concentration. For a standard IC₅₀ determination the data acquired is fit by the following four parameter equation using a nonlinear fitting program (e.g., Grafit 4):

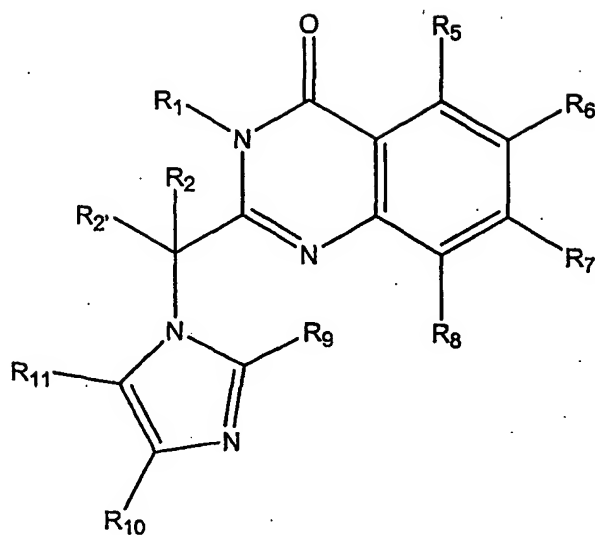
$$y = \frac{\text{Range}}{1 + \left(\frac{x}{\text{IC}_{50}} \right)^s} + \text{Background}$$

where y is the observed rate and x is the compound concentration.

What is claimed is:

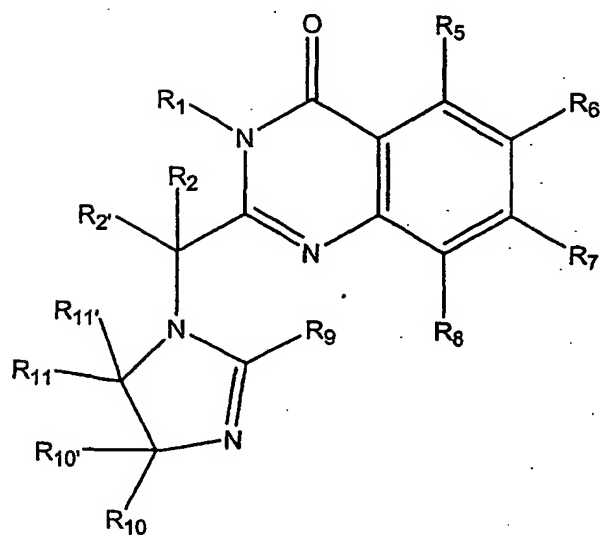
1. A compound chosen from:
compounds having the structure

5



Formula Ia

10 or



Formula Ib

15 wherein:

- R_1 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaralkyl-;
- R_2 and R_2' are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, optionally substituted heteroaryl-, and optionally substituted heteroaralkyl-; or R_2 and R_2' taken together form an optionally substituted 3- to 7-membered ring;
- R_5 , R_6 , R_7 and R_8 are independently chosen from hydrogen, optionally substituted alkyl-, optionally substituted alkoxy, halogen, hydroxyl-, nitro, cyano, dialkylamino, alkylsulfonyl-, alkylsulfonamido, alkylthio, carboxyalkyl-, carboxamido, aminocarbonyl-, optionally substituted aryl-, optionally substituted aryloxy, optionally substituted heteroaryl-, and optionally substituted heteroaryloxy;
- R_9 is chosen from hydrogen, optionally substituted alkyl-, optionally substituted aryl-, optionally substituted aralkyl-, and optionally substituted heteroaryl-; and
- R_{10} , $R_{10'}$, R_{11} , and $R_{11'}$ are independently hydrogen, optionally substituted alkyl-, optionally substituted aryl-, or optionally substituted aralkyl-, including single stereoisomers and mixtures of stereoisomers;
- pharmaceutically acceptable salts of a compound of Formula Ia or Ib;
- pharmaceutically acceptable solvates of a compound of Formula Ia or Ib; and
- pharmaceutically acceptable solvates of a pharmaceutically acceptable salt of a compound of Formula Ia or Ib.
2. A compound according to claim 1, wherein R_1 is selected from hydrogen, optionally substituted C_1 - C_8 alkyl-, optionally substituted aryl-, optionally substituted heteroaryl-, optionally substituted aryl- C_1 - C_4 -alkyl-, and optionally substituted heteroaryl- C_1 - C_4 -alkyl-.
3. A compound according to claim 2, wherein R_1 is selected from hydrogen, optionally substituted C_1 - C_4 alkyl-, optionally substituted phenyl- C_1 - C_4 -alkyl-, optionally substituted naphthalenylmethyl-, optionally substituted phenyl-, and naphthyl-.
4. A compound according to claim 3, wherein R_1 is optionally substituted phenyl- C_1 - C_4 -alkyl-, optionally substituted heteroaryl- C_1 - C_4 -alkyl-, or

naphthalenylmethyl-.

5. A compound according to claim 4, wherein R₁ is benzyl-.
6. A compound according to claim 1, wherein R₂' is hydrogen and R₂ is optionally substituted C₁-C₄ alkyl-.
- 5 7. A compound according to claim 6, wherein R₂ is chosen from methyl-, ethyl-, propyl-, butyl-, methylthioethyl-, methylthiomethyl-, aminobutyl-, (CBZ)aminobutyl-, cyclohexylmethyl-, benzyloxymethyl-, methylsulfanylethyl-, methylsulfanylmethyl-, and hydroxymethyl-, and R₂' is hydrogen.
8. A compound according to claim 7, wherein R₂' is hydrogen and R₂ is ethyl- or
10 propyl-.
9. A compound according to claim 8, wherein R₂ is i-propyl-.
10. A compound according to claim 1, wherein R₅, R₆, R₇, and R₈ are independently chosen from hydrogen, hydroxyl, halogen, C₁-C₄ alkyl-, C₁-C₄ alkoxy, and cyano.
- 15 11. A compound according to claim 10, wherein R₅, R₆, R₇, and R₈ are methoxy, hydrogen or halo.
12. A compound according to claim 11, wherein only one of R₅, R₆, R₇, and R₈ is not hydrogen.
13. A compound according to claim 1, wherein R⁹ is hydrogen; C₁-C₄ alkyl;
20 substituted C₁-C₄ alkyl-; aryl-; substituted aryl-; aryl-C₁-C₄-alkyl-; heteroaryl-; substituted heteroaryl-; or substituted aryl-C₁-C₄-alkyl-.
14. A compound according to claim 13, wherein R₉ is hydrogen; methyl-; ethyl-; propyl-; phenyl-; tolyl-; ethylphenyl-; halophenyl-; acetaminophenyl-; cyanophenyl-; halomethylphenyl-; polyhalophenyl-; methoxymethyl-; methoxyethyl-;
25 methoxyphenyl-; dimethoxyphenyl-; methylenedioxyphenyl-; trifluoromethylphenyl-; furyl-; thiophenyl-; pyridinyl-; halomethylpyridinyl-; isoxazolyl-; methylisoxazolyl-; dimethylaminophenyl-; diethylaminophenyl-; isopropylphenyl-; or quinoxalinyl-.
15. A compound according to claim 1, wherein R₁₀ and R₁₀' are independently selected from the group consisting of hydrogen; hydroxymethyl-; aminomethyl-;
30 acetaminomethyl-; (carboxymethyl-amino)-methyl-; aminoethyl-; acetaminomethyl-; (carboxymethyl-amino)-ethyl-; hydroxyethyl-; aminopropyl-; acetaminopropyl-; (carboxymethyl-amino)-propyl-; hydroxypropyl-; methyl-; ethyl-; and propyl-.
16. A compound according to claim 18, wherein R₁₁ and R₁₁' are independently

selected from the group consisting of hydrogen and optionally substituted C₁-C₄ alkyl-.

17. A compound according to claim 16, wherein R₁₁ and R_{11'} are hydrogen.
18. A compound of Formula Ia according to claim 1, wherein R₁ is benzyl-,
5 halobenzyl-, methoxybenzyl-, cyanobenzyl-, or naphthylmethyl-; R₂ is chosen from ethyl- and propyl-; R_{2'} is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is halogen; R₈ is hydrogen; and R₉ is substituted phenyl-; R_{9'} is hydrogen; R₁₀ is methyl-, hydrogen, or amino lower-alkyl-; and R₁₁ is hydrogen.
19. A compound of Formula Ib according to claim 1, wherein R₁ is benzyl-,
10 halobenzyl-, methoxybenzyl-, cyanobenzyl-, or naphthylmethyl-; R₂ is chosen from ethyl- and propyl-; R_{2'} is hydrogen; R₅ is hydrogen; R₆ is hydrogen; R₇ is halogen; R₈ is hydrogen; and R₉ is substituted phenyl-; R_{9'} is hydrogen; R₁₀ and R_{10'} are methyl-, hydrogen, or amino lower-alkyl-; and R₁₁ and R_{11'} are hydrogen.
20. A compound according to any one of claims 1-19 wherein R₂ and R_{2'} are each
15 attached to a stereogenic center having an R-configuration.
21. A composition comprising a pharmaceutical excipient and a compound of any one of claims 1-20.
22. A composition according to claim 21, wherein said composition further comprises a chemotherapeutic agent other than a compound of claim 1.
- 20 23. A composition according to claim 22, wherein said composition further comprises a taxane.
24. A composition according to claim 22, wherein said composition further comprises a vinca alkaloid.
25. A composition according to claim 22, wherein said composition further
25 comprises a topoisomerase I inhibitor.
26. A method of modulating KSP kinesin activity which comprises contacting said kinesin with an effective amount of a compound according to any one of claims 1 to 19.
27. A method of inhibiting KSP which comprises contacting said kinesin with an
30 effective amount of a compound according to any one of claims 1 to 19.
28. A method for the treatment of a cellular proliferative disease comprising administering to a subject in need thereof a compound according to any one of claims 1-19.

29. A method for the treatment of a cellular proliferative disease comprising administering to a subject in need thereof a composition according to any one of claims 21-25.
30. A method according to claim 28 or claim 29 wherein said disease is selected
5 from the group consisting of cancer, hyperplasias, restenosis, cardiac hypertrophy, immune disorders, and inflammation.
31. The use, in the manufacture of a medicament for treating cellular proliferative disease, of a compound according to any one of claims 1-19
32. The use of a compound as defined in claim 31 for the manufacture of a
10 medicament for treating a disorder associated with KSP kinesin activity.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/14787

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/454; C07D 413/02, 413/07.

US CL : 514/266.23; 544/284, 285

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/266.23; 544/284, 285

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ON-LINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P — A, P	US 2002/0169159 A1 (MEDINA et. al.) 14 November 2002 (14.11.2002), see the final products in Fig. 16.	1-10, 14, 15, 20, 21 — 11-13, 18, 19, 22-28, 31-32
X, P — A, P	US 2003/0055054 A1 (MEDINA et. al.) 20 March 2003 (20.03.2003), see the final products in Fig. 16.	1-10, 14, 15, 20, 21 — 11-13, 18, 19, 22-28, 31-32
A,E	US 2003/0091946 A1 (UCHIRA et. al.) 15 May 2003 (15.05.2003).	1-28, 31-32

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&"

document member of the same patent family

Date of the actual completion of the international search

23 July 2003 (23.07.2003)

Date of mailing of the international search report

29 AUG 2003

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/14787

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 29-30
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.